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Errata

Vol. 1949, page 3038, line 6*. *For* (I; R = Me, R = H) *read* (I; R = Me, R′ = H).

Vol. 1949, page 3039, line 25. *For* (VII; R = CHO, R′ = Me) *read* (VII; R = Me, R′ = CHO).

Vol. 1949, page 3277, lines 34 and 38. For 1 : 2 : 3-*Trimethoxy*-5-*methylnaphthalene* read 1 : 2 : 3-*Trimethoxy*-8-*methylnaphthalene*.

Vol. 1949, page 3349, line 20. *For* heptanone *read* heptenone.

Vol. 1949, page S233, line 21. *Before* and acetic anhydride (10 c.c.) *add* sodium iodide (1 g.),.

Vol. 1949, page S244, line 2*. *For* 2969 *read* 2696.

Vol. 1949, page S299, line 22. *For* molarity *read* molality.

Vol. 1949, page S299, line 17*. *For* molarities *read* molalities.

Vol. 1949, page S300, line 5* (twice). *For* Molarities *read* Molalities.

Vol. 1949, page S301, line 12 (twice). *For* Molarities *read* Molalities.

Vol. 1949, page S301, line 16*. *For* Molarity *read* Molality.

Vol. 1949, page S318, line 27. *For* 5·325 *read* 5·34.

Vol. 1949, page S321, line 22. *For* 5·325 *read* 5·34.

Vol. 1949, page S373, last line of footnote. *For* duration *read* durations.

Vol. 1950, page 23, line 15*. *For* −48° *read* +48°.

Vol. 1950, page 25, line 24*. *For* −48° *read* +48°.

Vol. 1950, page 60, line 10. *Formula* (1) *should read* $\dfrac{\int\psi(\mathbf{B}_{3u})H(E_g^+)\psi(\mathbf{E}_u^-)\mathrm{d}\tau}{E(\mathbf{B}_{3u})-E(\mathbf{E}_u^-)}$.

Vol. 1950, page 136, line 4*. *Before* 50% *insert* *p*-nitrobenzaldehyde in.

Vol. 1950, page 138, line 21. *For* 0·55 g. *read* 0·055 g.

Vol. 1950, page 173, line 2*. *For* Mrs. *read* Mr.

Vol. 1950, page 210, line 25. *For* 160° *read* 147°.

Vol. 1950, page 310, line 19. *For* $d^{249\cdot5}$ *read* $d^{24\cdot95}$.

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ERRATA.

Vol.	Page.	Line.	
1945	774	14	For $q_1 = q/z(1 + bp)$ read $q_1 = q/(1 + bp)$.
	774	16 *	For $q_1 = q/44(1 + 0{\cdot}038p)$ read $q_1 = q/(1 + 0{\cdot}038p)$.
1946	748	43	*For* $C_{24}H_{32}O_5$ *read* $C_{24}H_{32}O_2$.
1949	711	1 *	For 4-*Keto*-1 : 1-*dimethylpiperidinium* read 4-*Keto*-1 : 1-*diethylpiperidinium*.
	1279	18 *	*Formula* (VI.) *should read* $[\overset{+}{N}HMe_2\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot C_6H_4\cdot \overset{+}{N}HMe_2]\overset{-}{Br}_2$.
	1883	2 *	*For* nitroamines *read* nitroamides.
	2439	31 *	For 4-*phenyltetrahydrothiazine* read *tetrahydrothiazine*.
	2587	2 *	*For* 1-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*quinone *read* 1-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline.
	2825	Table I	For *β-naphthyl-2-chloroethylamine* read N-*β-naphthyl*-N-*methyl*-N-2-*chloroethylamine*.
	2998	35 *	*For* iodate *read* periodate.
1950	60	10	*Formula* (1) *should read* $\dfrac{\int\psi(\mathbf{B}_{2u})H(E_g^+)\psi(\mathbf{E}_u^-)d\tau}{E(\mathbf{B}_{2u}) - E(\mathbf{E}_u^-)}$.
	210	25	*For* 160° *read* 147°.

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1. *Puberulic and Puberulonic Acids. Part I. The Molecular Formula of Puberulonic Acid and Consideration of Possible Benzenoid Structures for the Acids.*

By R. E. Corbett, C. H. Hassall, A. W. Johnson, and A. R. Todd.

The molecular formula of puberulonic acid, recorded by earlier workers as $C_8H_4O_6$, has been revised to $C_9H_4O_7$. A possible trihydroxyformylbenzoic acid structure for puberulic acid has been shown to be untenable by the non-identity of 2 : 3 : 5-*trihydroxybenzaldehyde* with the decarboxylation product of puberulic acid. Benzenoid formulæ for these acids are therefore excluded.

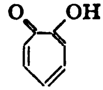
Puberulic and puberulonic acids were first isolated by Birkinshaw and Raistrick (*Biochem. J.*, 1932, **26**, 441) from cultures of the moulds *Penicillium puberulum* and *P. aurantio-virens* and the formulæ $C_8H_6O_6$ and $C_8H_4O_6$ respectively were assigned to them. Both compounds titrated as dibasic acids, and the almost colourless puberulic acid, m. p. 316—318°, could be separated from mixtures of the two as its diacetyl derivative, m. p. 212°, whereas the yellow puberulonic acid, m. p. 298°, was unaffected by acetylating agents. Puberulic acid formed a tetramethyl derivative with diazomethane, and diacetylpuberulic acid formed a dimethyl derivative under the same conditions, so that the molecule of puberulic acid contained four acidic groups of which at least two were enolic or phenolic hydroxyl groups. No evidence was obtained for the presence of a carbonyl group, and the authors were unable to suggest a satisfactory structure either for puberulic or for puberulonic acid. A little later Barger and Dorrer (*ibid.*, 1934, **28**, 11) carried out a further investigation of the two acids but likewise were unable to advance structural formulæ to explain all of the experimental results. They showed that puberulic acid almost certainly contained a carboxyl group since it readily lost carbon dioxide when heated, yielding a crystalline product, $C_7H_6O_4$. Puberulonic acid changed from yellow through pink to colourless in the course of neutralisation with sodium hydroxide and, on the assumption of a formula $C_8H_4O_6$, irregular values were given for the basicity : a value of 2·3 was obtained when the acid was titrated directly, whereas back titration of alkaline solutions gave values varying from 2·9 to 3·5. This seemed to suggest the presence of a lactone or pseudo-acid grouping. In a footnote to their paper Barger and Dorrer (*loc. cit.*) stated that Dr. Hoyer had obtained evidence that puberulonic acid is structurally related to puberulic acid but the nature of this evidence has never been divulged.

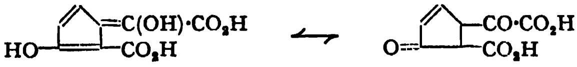
No further work on the chemistry of these compounds has been published. Oxford, Raistrick, and Smith (*Chem. and Ind.*, 1942, **61**, 485) have described the isolation of the same acids from *P. Johannioli* Zaleski and *P. cyclopium–viridicatum* series and have reported that these mould metabolic products have a significant antibiotic activity against various Gram-positive organisms. Dewar (*Nature*, 1945, **155**, 479) suggested that puberulic acid might be a hydroxystipitatic acid but adduced no evidence to support this formulation; stipitatic acid itself was claimed by the same author (*ibid.*, p. 50) to be a derivative of tropolone (I). More recently McGowan (*Chem. and Ind.*, 1947, **66**, 205) advanced structures (II) and (III) for puberulic and puberulonic acid respectively, but again without experimental support.

In the present work, the two acids were isolated from the culture medium of *P. aurantio-virens* essentially as described by Birkinshaw and Raistrick (*loc. cit.*), although the yield was increased by using a relatively high temperature (30°) for the growth of the mould. The formula for puberulonic acid, $C_8H_4O_6$, put forward by earlier workers has been amended to $C_9H_4O_7$, the results of analyses being supported by the preparation of a *complex*, $C_9H_4O_7,C_5H_5N$, with pyridine, of a condensation *product*, $C_{15}H_8O_5N_2$, with *o*-phenylenediamine, and by experiments on the hydrolysis of the acid. When puberulonic acid is heated in dilute sulphuric acid solution, one molecular equivalent of carbon dioxide is evolved and puberulic acid is obtained in quantitative yield:

$$C_9H_4O_7 + H_2O \longrightarrow C_8H_6O_6 + CO_2$$

Thus the relationship between the acids has been finally established.


(I.)



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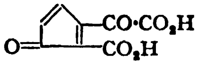

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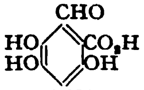
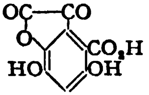


(IV.)



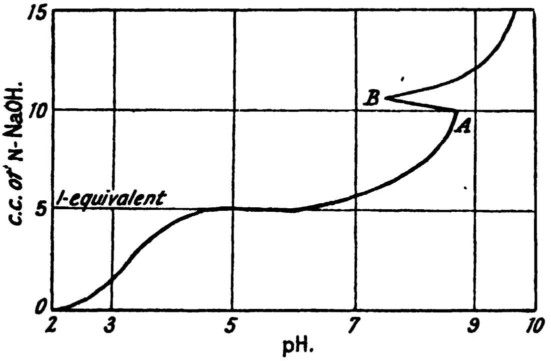
(V.)

The potentiometric titration (Fig. 1) of puberulonic acid gives some support to the suggestion that a lactone grouping is present in the molecule, for during the neutralisation of the free acid a decrease in the pH was apparent on leaving the solution to stand or on further slow addition of small amounts of alkali at any point between about pH 7 and pH 10. An illustration of this effect is shown in Fig. 1.

Since in many respects puberulic acid has properties not unlike those of an aromatic compound, it seemed advisable to consider at the outset whether the evidence available supported a benzenoid formula. Birkinshaw and Raistrick (*loc. cit.*) and Barger and Dorrer (*loc. cit.*) had rejected the possibility that puberulic acid might be a dihydroxybenzenedicarboxylic acid because the decarboxylation product they obtained was not identical with any of the dihydroxybenzoic acids. Several pieces of evidence suggest that puberulic acid contains three phenolic hydroxyl groups; the dimethyl derivative formed on alkaline hydrolysis of "tetramethylpuberulic acid" gives a strong ferric reaction, and the *diacetyl* derivative of decarboxylated puberulic acid likewise gives an immediate coloration with ferric chloride. Furthermore, the isolation of a compound containing only one carbomethoxy-group from the hydrogenation product of the tetramethyl derivative suggests that puberulic acid itself contains only one carboxyl group. For these reasons structure (IV) for puberulic acid appeared worthy of consideration; on this basis the formulation of puberulonic acid as (V) might account for its condensation with *o*-phenylenediamine in the manner of an α-diketone, its yellow colour, and, if somewhat less readily, its conversion into puberulic acid on acid hydrolysis.

FIG. 1.

Potentiometric titration of puberulonic acid. The portion A—B *of the curve shows the decrease in pH during slow addition of alkali.*



The most serious objections to formulæ (IV) and (V) were that no carbonyl derivatives of either puberulic or decarboxylated puberulic acid could be prepared and that puberulonic acid could not be acetylated, but nevertheless it was felt that the hypothesis should be tested by comparison of decarboxylated puberulic acid with 2 : 3 : 5-*trihydroxybenzaldehyde*. This aldehyde had not been previously described and it has now been obtained in 20% overall yield by the Rosenmund reduction of 2 : 3 : 5-triacetoxybenzoyl chloride and subsequent hydrolysis of the 2 : 3 : 5-*triacetoxybenzaldehyde* produced. A comparison of the properties of 2 : 3 : 5-trihydroxybenzaldehyde and the decarboxylation product of puberulic acid shows that there is little resemblance between them (Table I). The ultra-violet absorption spectra of the two compounds are shown in Fig. 2, and those of puberulic and puberulonic acids in Fig. 3.

The other trihydroxybenzaldehydes have been described in the literature and all are different from the decarboxylation product of puberulic acid. The only possible benzenoid structures, $C_8H_6O_6$, which accommodate two phenolic groups and a carboxyl group are those of the dihydroxybenzenedicarboxylic acids and the trihydroxyformylbenzoic acids (*e.g.*, IV); these structures have now been shown to be untenable for puberulic acid. Other ring structures must be considered and we have, therefore, taken up afresh degradative studies on both puberulic and puberulonic acids; the results will be presented in a separate communication.

TABLE I.

	2 : 3 : 5-Trihydroxybenzaldehyde.	Decarboxylated puberulic acid.
Colour	Canary yellow	Colourless
M. p.	187° (decomp.)	237—238°
2 : 4-Dinitrophenylhydrazone	Orange-red derivative	No reaction
Ferric reaction	Olive green	Deep blood-red
Condensation with ω-hydroxyacetophenone	Wine-red colour	No reaction
Coloration with aqueous sodium hydroxide	Golden-yellow	Light brown; rapidly darkens

2 : 3 : 5-Trihydroxybenzaldehyde was also prepared, albeit in poor yield, by oxidation of α-resorcylaldehyde with potassium persulphate. There are several recorded examples of the preparation of aromatic hydroxyaldehydes by this reaction (*e.g.*, Baker and Brown, *J.*, 1948, 2303) but this is the first instance in which it has been used to hydroxylate a dihydroxybenzaldehyde. The oxidation was carried out in an atmosphere of nitrogen and the product isolated by the method of Baker, Brown, and Scott (*J.*, 1939, 1922). In connection with the synthesis of 2 : 3 : 5-triacetoxybenzoyl chloride required for the preparation of the trihydroxybenzaldehyde, a number of routes to 2 : 3 : 5-*trihydroxybenzoic acid* were investigated and it was eventually obtained in 15% yield by persulphate oxidation of α-resorcylic acid. The conditions for this oxidation were worked out in preliminary experiments on the oxidation of salicylic acid to gentisic acid (cf. Schering, D.R.-P. 81,297; Graebe and Martz, *Annalen*, 1905, **340**, 213; Nandor and Mauthner, *J. pr. Chem.*, 1940, **156**, 150) which was itself required for another possible route to 2 : 3 : 5-trihydroxybenzoic acid *via* 3-amino-2-acetylgentisic acid. This latter compound, in the form of its *ethyl* ester, was diazotised by the method of Hodgson and Walker (*J.*, 1933, 1620), but heating the diazonium salt with 60% sulphuric acid under reflux gave gentisic acid (30%). This behaviour recalls that of aminogallic acid which under similar conditions is deaminated giving gallic acid (Power and Shedden, *J.*, 1902, **81**, 73). On the other hand 5-aminosalicylic acid was successfully converted into gentisic acid by this method.

FIG. 2.

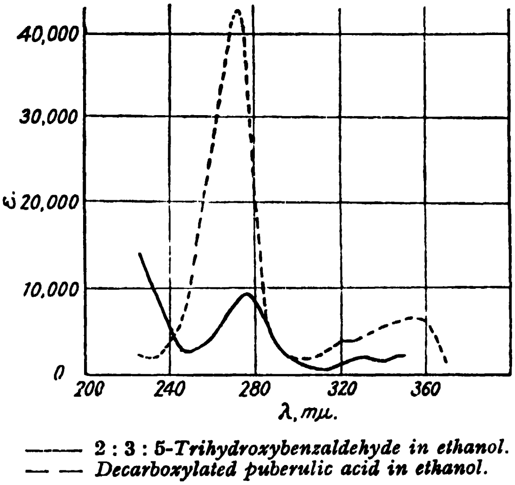
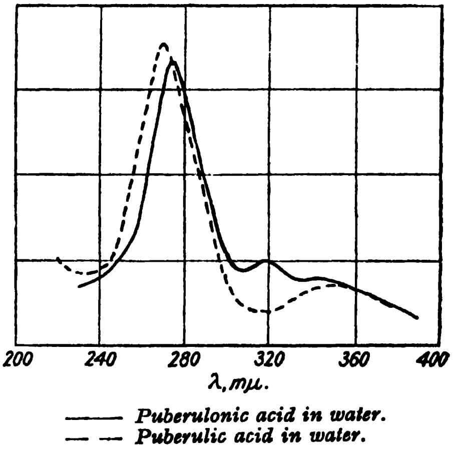
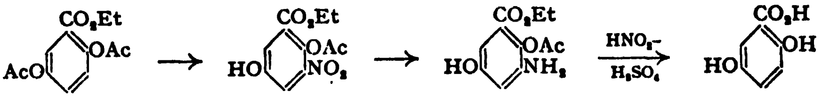


FIG. 3.





EXPERIMENTAL.

Puberulic and Puberulonic Acid.—The acids were isolated from the culture medium of *Penicillium aurantio-virens* by a modification of the method of Birkinshaw and Raistrick (*loc. cit.*). The mould was grown at 30° rather than at 24—25° as previously recommended, thereby increasing the yield of the acid and decreasing the production of mould mycelium. After separation of the medium from the associated mycelial mat, and clarification of the solution by passage through a Sharples centrifuge, the pH was adjusted to 5·5 by the addition of sodium hydroxide solution. N-Nickel sulphate solution (900 c.c. for each 15 l. of mould solution) was then added, the pH again brought to 5·5, and the red nickel complex which separated was collected on the Sharples centrifuge. Decomposition of the nickel complex and separation of the mixed acids were carried out by the method of Barger and Dorrer (*loc. cit.*). From 30 l. of culture fluid 12 g. of mixed puberulic and puberulonic acid were obtained.

Puberulic acid (2 g.) was crystallised from methanol (50 c.c.), dissolution being effected in a hot extraction apparatus. The acid formed almost colourless plates, m. p. 318—320° (Found : C, 48·6; H, 3·0. Calc. for $C_8H_6O_6$: C, 48·5; H, 3·05%). The ultra-violet absorption of puberulic acid showed maxima at 2700 A. (ε, 35,200) and 3500 A. (ε, 7,160).

Puberulonic acid crystallised from ethyl malonate as fine yellow needles, m. p. 298° (decomp.) (Found : C, 48·0; H, 2·0. $C_9H_4O_7$ requires C, 48·2; H, 1·8. $C_8H_4O_6$ requires C, 49·0; H, 2·1%). Light absorption : Maxima at 2745 A. and 3170 A. (ε, 33,400 and 9,900 respectively). For the potentiometric titration of puberulonic acid, a well stirred suspension of the acid (1·12 g.) in water (20 c.c.) was neutralised with N-sodium hydroxide. The titration was followed potentiometrically by means of a calomel electrode–glass electrode system. The results are recorded in Fig. 1. The solution became pink at pH 7—8. This colour change was most marked after the addition of two equivalents of sodium hydroxide, and after the addition of three equivalents of alkali (pH 9·6) the solution remained orange in colour. No colour change was observed during the back-titration, and puberulonic acid was recovered unchanged from the acid solution. Barger and Dorrer (*loc. cit.*) claimed that the solution became colourless at pH 8—9.

Condensation of Puberulonic Acid with o-*Phenylenediamine.*—The acid (112 mg.) and *o*-phenylenediamine (60 mg.) were dissolved in just sufficient ethanol and heated under reflux for 4 hours, during which time a vermilion-red crystalline solid (125 mg.) separated. This *product* charred without melting on being heated to 350° and it was soluble with difficulty in water and organic solvents (Found: C, 60·6; H, 3·0; N, 9·3. $C_{15}H_8O_5N_2$ requires C, 60·8; H, 2·7; N, 9·4%).

Puberulonic Acid–Pyridine Complex.—Puberulonic acid (90 mg.) was heated with pyridine (2 c.c.) on a water-bath for 6 hours. Excess of pyridine was removed under reduced pressure, and the residual yellow solid was extracted with acetone to give relatively soluble unchanged puberulonic acid (10 mg.), leaving an insoluble *product* (70 mg.) which formed yellow needles, m. p. 257—258° (decomp.), from glacial acetic acid (Found : C, 55·5; H, 3·2; N, 4·6. $C_9H_4O_7,C_5H_5N$ requires C, 55·4; H, 3·0; N, 4·6%).

Conversion of Puberulonic Acid into Puberulic Acid.—A continuous stream of nitrogen, freed from carbon dioxide and oxygen, was passed through a boiling suspension of puberulonic acid (295 mg.) in 2N-sulphuric acid (50 c.c.). The carbon dioxide evolved in the reaction was collected quantitatively in barium hydroxide solution (90 c.c. of N/10) and after 8 hours the excess of barium hydroxide was determined by titration. Continuation of the hydrolysis for a further 2 hours did not change the titre (volume of barium hydroxide neutralised by carbon dioxide, 28 c.c.; calc. for 1 molar equivalent of carbon dioxide, 30 c.c.). The brown crystalline solid (243 mg.) formed in the course of reaction was separated and mixed with a further small quantity of solid (25 mg.) obtained by continuous ether extraction of the filtrate for 8 hours. The crude mixture, m. p. 305°, was repeatedly crystallised from acetone to give a faintly yellow micro-crystalline powder, m. p. 315° alone or mixed with an authentic specimen of puberulic acid (Found : C, 48·8; H, 3·2%).

Hydrogenation of Tetramethylpuberulic Acid (cf. Barger and Dorrer, *loc. cit.*).—Tetramethylpuberulic acid (534 mg.), m. p. 112°, was hydrogenated in pure glacial acetic acid at atmospheric temperature and pressure with a platinum catalyst. Six moles of hydrogen were absorbed and the solution was decolorised after the addition of 5 moles. The residue (500 mg.) obtained on removal of the acetic acid under reduced pressure was treated with water (5 c.c.), and the solution extracted with ether (2 × 10 c.c.). When the residual aqueous solution was treated with 2 : 4-dinitrophenylhydrazine a voluminous red precipitate separated. This precipitate was amorphous and oxidised in air; all attempts to purify it were unsuccessful. The ethereal extract was dried and evaporated, yielding a light-coloured oil (260 mg.) which on distillation gave a volatile fraction (160 mg.) and a residue which decomposed when further heated. The volatile fraction was redistilled; it had b. p. 120—125°/0·1 mm. and left only a trace of residue [Found : C, 59·7; H, 8·9; sap. val., 202, 204; active H (Zerewitinoff), 0·30%. $C_8H_{15}O_2(CO_2CH_3)$ requires C, 59·5; H, 8·9%; sap. val., 202; 1 active H, 0·49%].

Acetylation of Decarboxylated Puberulic Acid.—Decarboxylated puberulic acid (150 mg.) (Barger and Dorrer, *loc. cit.*), acetic anhydride (1·0 g.), and sodium acetate (0·6 g.) were heated under reflux at 140—150° for 30 minutes. The mixture was then diluted with water (20 c.c.) and acidified with hydrochloric acid. The clear solution was evaporated under reduced pressure at 25° and the residue extracted with ether. Removal of the solvent from the ethereal extract gave a brown resin which was distilled (110°/0·4 mm.) to give a light-yellow resin (70 mg.). The latter crystallised from ether–light petroleum (b. p. 40—60°) as colourless prisms, m. p. 124·5—125° [Found : C, 55·1; H, 4·4. $C_7H_4O_2(O{\cdot}CO{\cdot}CH_3)_2$ requires C, 55·4; H, 4·2%]. The *diacetyl* derivative gave an immediate purple coloration with ferric chloride.

Gentisic Acid.—(a) *From salicylic acid.* Salicylic acid (18 g., 1 mol.) was dissolved in water (375 c.c.) containing sodium hydroxide (25 g., 5 mols.). The solution was brought to 35—40° and maintained at this temperature during the course of the experiment. Potassium persulphate (35 g., 1·1 mols.) was added portionwise during 3 hours. The reaction mixture, which rapidly developed a deep chocolate-brown colour, was left for 36 hours at room temperature and then acidified with concentrated hydrochloric acid until just acid to Congo-red. This solution was extracted with ether (3 × 300 c.c.), and the combined ethereal extracts dried and evaporated to yield unchanged salicylic acid (9·5 g.). A further quantity of hydrochloric acid (100 c.c.) was added to the mother-liquors which were then kept at room temperature for 48 hours and extracted with ether (5 × 300 c.c.). The combined ethereal extracts were dried, clarified with charcoal, and evaporated, to yield crude gentisic acid (9·5 g.), m. p. 195—198°, usually of sufficient purity for conversion into the ester. Further purification was effected by recrystallisation of the crude acid from water (charcoal).

(b) *From 5-aminosalicylic acid.* 5-Aminosalicylic acid (Puxeddu, *Gazzetta*, 1929, **59**, 10) (4·3 g.) was dissolved in concentrated sulphuric acid (30 c.c.) and the solution cooled to below 10°. A solution of sodium nitrite (2·5 g.) in concentrated sulphuric acid (15 c.c.) was prepared by stirring the nitrite into the acid at 0° and completing dissolution by raising the temperature to 70°. After cooling to 5°, this solution was stirred into the sulphuric acid solution of 5-aminosalicylic acid, and the mixture added portionwise to glacial acetic acid (55 c.c.) during an hour, the temperature being kept below 20°. Anhydrous ether (50 c.c.) was then added, whereupon a fine white precipitate of sodium sulphate was obtained and after 3 hours at 0° this was removed (4·0 g.). A further quantity of ether (300 c.c.) was stirred into the mixture, and after 24 hours at 0° a large quantity of feathery crystals had separated which were shown to be the diazonium salt from 5-aminosalicylic acid. The crystalline solid was separated, and washed with 50% glacial acetic acid–ether (20 c.c.) and finally with ether (20 c.c.). The still moist crystals were dissolved in sulphuric acid (15 c.c. of 20%), and the solution added dropwise to boiling sulphuric acid (70 c.c. of 60%). After the mixture had been heated under gentle reflux for 45 minutes, evolution of nitrogen ceased and the solution was cooled and extracted with ether (5 × 100 c.c.). The dried ethereal extract was clarified with charcoal and evaporated to yield gentisic acid (2·1 g.), m. p. 196—198°.

2 : 3 : 5-*Trihydroxybenzoic Acid.*—The experimental procedure was similar to that described for gentisic acid. α-Resorcylic acid (32 g.) yielded unchanged starting material (12 g.) and crude 2 : 3 : 5-*trihydroxybenzoic acid* (10 g.). The crude acid was washed with ice-water and recrystallised repeatedly from water (charcoal) to give the pure acid (2·5 g.) as lemon-yellow needles, m. p. 223° (decomp.) (Found : C, 49·8; H, 3·6. $C_7H_6O_5$ requires C, 49·4; H, 3·5%). The acid gave a reddish-brown colour with ferric chloride.

2 : 3 : 5-*Triacetoxybenzoic Acid.*—2 : 3 : 5-Trihydroxybenzoic acid (7·2 g.), sodium acetate (15 g.), and acetic anhydride (30 c.c.) were heated initially at 85—90° until the acid dissolved, and then under reflux for 3 hours. The cooled solution was poured into water (150 c.c.), acidified with sulphuric acid (21 c.c. of 10N.), and extracted with ether (6 × 200 c.c.). After removal of the ether, the *triacetoxy-acid* remained as a white crystalline solid (11·4 g.) and after recrystallisation from benzene had m. p. 139—140° (Found : C, 53·1; H, 4·1. $C_{13}H_{12}O_8$ requires C, 52·7; H, 4·1%).

2 : 3 : 5-*Triacetoxybenzoyl Chloride.*—2 : 3 : 5-Triacetoxybenzoic acid (6·1 g.) and thionyl chloride (20 c.c.) were heated on a water-bath under reflux for 40 minutes, by which time evolution of sulphur dioxide had ceased. Removal of the excess of thionyl chloride *in vacuo* gave a gum which crystallised slowly in the ice-chest. The crystals were washed with light petroleum (b. p. 60—80°), and dried on porous tile and then in a vacuum-desiccator over phosphoric oxide. The product (6·3 g.) had m. p. 70—75°. Further purification could not be effected; attempted micro-distillation caused decomposition, and crystallisation could not be achieved from light petroleum, benzene, or xylene. With *p*-toluidine, the acid chloride gave 2 : 3 : 5-*trihydroxybenzo*-p-*toluidide*, which had m. p. 166—167° after recrystallisation from ethanol (Found : C, 62·7; H, 5·2; N, 3·7. $C_{20}H_{19}O_7N$ requires C, 62·3; H, 5·0; N, 3·6%).

2 : 3 : 5-*Triacetoxybenzaldehyde.*—2 : 3 : 5-Triacetoxybenzoyl chloride (5·5 g.), xylene (30 c.c.), and palladium–barium sulphate (2 g.; 2% of Pd) were placed in a 150-c.c. round-bottomed flask equipped with a reflux condenser, a sealed Hershberg stirrer, and a gas inlet tube reaching to the bottom of the flask. A brisk stream of hydrogen was passed through the rapidly stirred mixture, and the temperature raised to reflux. The exit gases were bubbled into water, and the evolved hydrogen chloride titrated from time to time. After 5 hours no more hydrogen chloride was formed, 85% of the theoretical amount having been collected. After cooling, catalyst was removed and washed thoroughly with dry ether (150 c.c.). The ether and xylene extracts were combined, washed with sodium hydrogen carbonate solution (50 c.c.) and then water (2 × 50 c.c.), and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the resinous residue crystallised partly on prolonged cooling. The crystals were washed with dry ether (10 c.c.) and recrystallised first from benzene and then from ether–light petroleum (b. p. 40—60°) or from benzene. The *product* (3·2 g.) had m. p. 90—91° (Found : C, 55·6; H, 4·6. $C_{13}H_{12}O_7$ requires C, 55·7; H, 4·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid (90%) in canary-yellow feathery needles, m. p. 240° (decomp.) (Found : C, 49·3; H, 3·6; N, 12·5. $C_{19}H_{16}O_{10}N_4$ requires C, 49·7; H, 3·3; N, 12·2%).

2 : 3 : 5-*Trihydroxybenzaldehyde.*—(a) *From* 2 : 3 : 5-*triacetoxybenzaldehyde.* The triacetoxy-aldehyde (1·2 g.) and anhydrous potassium acetate (4·8 g.) were dissolved in dry methanol (50 c.c.) and heated under reflux in a current of hydrogen for 2 hours. The cooled solution was acidified to Congo-red with sulphuric acid (30 c.c. of 2N.) and kept at 0° for 3 hours. Sodium sulphate was separated by filtration, and the filtrate extracted with ether (5 × 50 c.c.). The extract was dried and the solvent removed *in vacuo*, leaving a black tar. This was dried by distillation with benzene and again extracted with dry ether (100 c.c.). Removal of the ether gave a lemon-yellow solid (200 mg.) which was further purified by sublimation at 130°/10^{-3} mm., giving a yellow micro-crystalline solid, m. p. 187° (decomp.), alone or mixed with the product prepared by persulphate oxidation (see below).

(b) *From α-resorcylaldehyde.* α-Resorcylaldehyde (22·5 g., 1 mol.) was dissolved in aqueous sodium hydroxide [32·6 g. (5 mols.) in 450 c.c. of water] which had been freed from air by passing nitrogen through it for some time. The solution was warmed to 35—40° and maintained at this temperature during the course of the experiment. Potassium persulphate (48 g., 1·1 mols.) was added in portions during 3 hours, the reaction mixture rapidly becoming deep chocolate-brown. The mixture was set aside at room temperature for 36 hours, and then acidified with concentrated hydrochloric acid until just acid to Congo-red. The copious chocolate-coloured precipitate which separated was collected (18 g.); it was mainly unchanged starting material. The mother-liquors were extracted with ether

(3 × 300 c.c.), and the extract gave a further small amount of unchanged starting material. Concentrated hydrochloric acid (150 c.c.) and ether (300 c.c.) were added to the aqueous layer, and the mixture was heated under reflux on a water-bath at 70° for 1 hour. The ethereal layer was separated, dried, and clarified with charcoal. After removal of the solvent the dark-coloured residue was extracted with boiling benzene, and the benzene extract on cooling deposited a small amount of yellow crystalline material (20 mg.). Further extraction of the mother-liquors with chloroform (4 × 300 c.c.) and removal of the chloroform under reduced pressure gave a second crop of crude material (20 mg.). Purification by sublimation at 130°/10^{-2} mm. gave a yellow micro-crystalline solid which charred at 160° and decomposed at 187° (Found : C, 54·9; H, 4·0. $C_7H_6O_4$ requires C, 54·5; H, 3·9%).

The *aldehyde* gave an olive-green colour with ferric chloride and a wine-red colour (pyrylium salt) with ω-hydroxyacetophenone under the conditions used in anthocyanin synthesis (*e.g.*, Robinson and Todd, *J.*, 1932, 2293). The 2 : 4-*dinitrophenylhydrazone*, m. p. >255° (decomp.), was very sparingly soluble in the common organic solvents (Found : N, 16·8. $C_{13}H_{10}O_7N_4$ requires N, 16·8%).

2-*Hydroxy*-3 : 5-*dimethoxybenzoic Acid.*—2 : 3 : 5-Trihydroxybenzoic acid (500 mg.) and methyl sulphate (6 c.c.) were stirred vigorously during dropwise addition of 5% potassium hydroxide solution. The addition was carried out at such a rate that the solution remained acid to litmus. A slight excess of potassium hydroxide solution was then added and the mixture heated at 70° for 1½ hours. The cooled mixture was acidified with 3N-hydrochloric acid and continuously extracted with ether for 6 hours. The ethereal extract was dried and then decolorised with charcoal, and the solvent removed *in vacuo*, yielding a brown solid. After two recrystallisations from water this gave colourless needles, m. p. 180·5° (Found : C, 54·7; H, 5·6. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%). The acid gave a deep greenish-blue ferric chloride reaction. This *acid* appeared to be identical with the hydroxydimethoxybenzoic acid obtained by Calam, Clutterbuck, Oxford, and Raistrick (*Biochem. J.*, 1947, **41**, 458) in the course of their degradation of methylated geodin.

Ethyl Diacetylgentisate.—Ethyl gentisate (21·5 g.; Juch, *Monatsh.*, 1905, **26**, 841) was dissolved in acetic anhydride (115 c.c.), concentrated sulphuric acid (2 c.c.) added, and the mixture set aside at room temperature for 36 hours. The solution was poured into ice–water (400 c.c.) and set aside in the ice-chest; the colourless oil which separated deposited crystals of the *diacetyl* ester (27·0 g.), which had m. p. 69·5° after recrystallisation from light petroleum (b. p. 60—80°) (Found : C, 58·6; H, 5·2; *O*-Ac, 34·1. $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3; *O*-Ac, 32·3%).

Ethyl 3-*Nitro*-2-*acetylgentisate.*—Ethyl diacetylgentisate (14·8 g.) was added in small portions during 90 minutes to well-stirred fuming nitric acid (14·3 c.c.; *d*, 1·5) maintained at 10—15° by ice-cooling. After addition was complete, the mixture was set aside for 40 minutes and the temperature allowed to rise to 20°. The mixture was then poured on crushed ice, whereupon the *nitro*-ester separated as an amorphous solid. Crystallisation from 50% ethanol (charcoal) yielded fine lemon-yellow needles (7·5 g.), m. p. 104·5° (Found : C, 49·3; H, 4·0; N, 5·3. $C_{11}H_{11}O_7N$ requires C, 49·0; H, 4·1; N, 5·2%).

Ethyl 3-*Amino*-2-*acetylgentisate.*—The foregoing nitro-ester (5 g.) was dissolved in methanol (300 c.c.) and hydrogenated using a Raney nickel catalyst (3 g.) at atmospheric pressure. The hydrogen uptake, which was slightly in excess of the calculated value for the hydrogenation of the nitro-group to an amino-group, was complete in 2 hours. After the wine-red solution had been decolorised with charcoal, methanol was removed *in vacuo* to yield the *amino*-ester (3·7 g.) as colourless plates, m. p. 139·5—140° after crystallisation from 80% methanol (Found : C, 55·4; H, 5·2; N, 6·0; *O*-Ac, 21·0. $C_{11}H_{13}O_5N$ requires C, 55·2; H, 5·4; N, 5·9; *O*-Ac, 18·0%).

Diazotisation and Hydrolysis of Ethyl 3-*Amino*-2-*acetylgentisate.*—The above amino-ester (1·25 g.), dissolved in glacial acetic acid (12·5 c.c.), was stirred into a mixture of sodium nitrite (0·6 g.) and concentrated sulphuric acid (6·5 c.c.), the temperature being kept below 15° by external cooling. The mixture was allowed to warm to room temperature, and after 30 minutes diazotisation was complete as shown by coupling tests with α-resorcylic acid. The solution was diluted with an equal volume of water and added dropwise to boiling sulphuric acid (50 c.c. of 60%) during 10 minutes. After cooling, the solution was continuously extracted with ether for 6 hours, and the ethereal extract dried and clarified with charcoal. Evaporation yielded crude gentisic acid (0·22 g.). Purified by sublimation it had m. p. 200° alone or mixed with an authentic specimen.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 26th,* 1949.]

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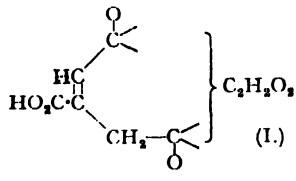
2. *Puberulic and Puberulonic Acids. Part II. Structure.*

By R. E. CORBETT, A. W. JOHNSON, and A. R. TODD.

Oxidation of puberulic acid with alkaline hydrogen peroxide yields aconitic acid. On the basis of this and other evidence, puberulic acid is formulated as 6 : 7-dihydroxytropolone-4-carboxylic acid (II), or one of its tautomeric forms. The properties of puberulonic acid, in particular its ready conversion into (II) in boiling aqueous solution, indicate that it has structure (VI), although a final decision between this and an isomeric structure containing a γ- rather than a δ-lactone grouping cannot yet be made.

PRELIMINARY work on the structure of the mould products, puberulic and puberulonic acids (Birkinshaw and Raistrick, *Biochem. J.*, 1932, **26**, 441; Barger and Dorrer, *ibid.*, 1934, **28**, 11) suggested that they had the molecular formulæ $C_8H_6O_6$ and $C_8H_4O_6$ respectively, but in Part I of this series (preceding paper) we amended the formula of puberulonic acid to $C_9H_4O_7$. The properties of puberulic acid as outlined in the previous paper indicate that it contains a carboxyl and three enolic groupings, but no direct evidence has been obtained for the presence of a free carbonyl group. It is apparent that the puberulic acid molecule must contain therefore the equivalent of five double bonds if the remaining oxygen atom is present as an ether linkage, or four double bonds if it is present as a masked carbonyl group. The nature of the ultra-violet absorption spectrum (preceding paper) and the facts that puberulic acid neither absorbs bromine from an acetic acid solution nor forms an adduct with maleic anhydride eliminate possible open-chain structures. In any case, the accommodation of at least four double bonds in an open chain of seven carbon atoms (allowing for the carboxyl group) would require the presence of acetylenic or cumulative ethylenic linkages.

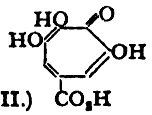
Important evidence on the nature of the cyclic system present in puberulic acid has been gained from oxidative degradation. Except for carbon dioxide, no identified products had been previously obtained from the oxidation of puberulic acid with, *e.g.*, permanganate, chromic acid, neutral hydrogen peroxide, alkaline hydrogen peroxide, or iodine and potassium hydroxide (Barger and Dorrer, *loc. cit.*). We have repeated the oxidation with alkaline hydrogen peroxide and have obtained aconitic acid in 40% yield; the identity of this product has been confirmed by direct comparison with an authentic specimen and by its hydrogenation to tricarballylic acid. On the other hand, oxidation with nitric acid gave only oxalic acid (1 mole) and carbon dioxide, and ozonolysis gave carbon dioxide (5·2 moles) with a small amount of an unidentified non-volatile acidic residue. This formation of aconitic acid establishes the relative positions of six of the eight carbon atoms of puberulic acid, and the molecule may now be represented as (I): A six-membered ring in puberulic acid would necessarily be benzenoid, and benzenoid structures have already been shown to be untenable (preceding paper). Thus, if the acid is monocyclic, there must be present either a five-membered or a seven-membered ring, and, since structures based on these systems could not accommodate the equivalent of four double bonds, the unplaced oxygen must be embodied in an inert carbonyl group rather than in an ether linkage. This argument also eliminates structures containing an oxygen-heterocyclic ring. A further theoretical possibility would be a formula based on the *bicyclo*[0 : 1 : 4]heptane system, but no reasonable structures can be devised which are derived either from this bicyclic system or from a monocyclic five-membered ring and at the same time account for the formation of aconitic acid by oxidation. Of seven-membered ring structures based on (I), the only possibility is (II) (or one of its tautomeric forms), according to which the acid is formulated as a derivative of *cyclo*heptatrienolone (tropolone) (III).



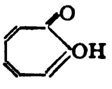
(I.)

The occurrence of tropolone derivatives in Nature is now well established, *e.g.*, the thujaplicins (Erdtman *et al.*, *Nature*, 1948, **161**, 719; *Acta Chem. Scand.*, 1948, **2**, 625, 639, 644), colchicine (Dewar, *Nature*, 1945, **155**, 141, 479; Arnstein *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1669; Lettré, *Angew. Chem.*, 1947, **59**, *A*, 218), and purpurogallin (Barltrop and Nicholson, *J.*, 1948, 116; Haworth, Moore, and Pauson, *ibid.*, p. 1045) which occurs as its glucoside, eriophyesin. There is also evidence that stipitatic acid, a mould product of *Penicillium stipitatum* (Birkinshaw, Chambers, and Raistrick, *Biochem. J.*, 1942, **36**, 242), is a hydroxytropolonecarboxylic acid (Dewar, *Nature*, 1945, **155**, 50; Corbett, Johnson, and Todd, unpublished work), and indeed Dewar (*loc. cit.*) has suggested, although without any experimental evidence, that puberulic acid might be a hydroxystipitatic acid.

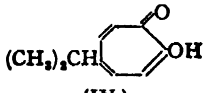
Characteristic features of the various tropolones hitherto examined have been (i) the inert carbonyl group which gives no characteristic reactions, (ii) the formation of substitution rather than addition products with bromine, and (iii) the formation of benzenoid derivatives containing one extra carboxy-group on fusion with potassium hydroxide. Reactions (i) and (ii) are shown by puberulic acid, but the potassium hydroxide fusion has so far failed to yield an aromatic product. The acid is unchanged by potassium hydroxide below 320°; above this temperature,



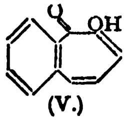
(II.)



(III.)



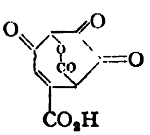
(IV.)

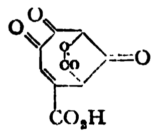


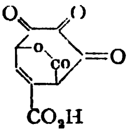
(V.)

gas is evolved and considerable charring occurs, but no recognisable product has been isolated. In this connection, it is interesting to note that, whereas γ-thujaplicin (IV) was converted with potassium hydroxide into *p*-*iso*propylbenzoic acid at 230° (Erdtman *et al.*, *loc. cit.*), and benztropolone (V) into α-naphthoic acid at 185° (Cook and Somerville, *Nature*, 1949, **163**, 410), stipitatic acid, a monohydroxytropolone derivative, required to be heated to 300° to give 5-hydroxy*iso*phthalic acid (Birkinshaw, Chambers, and Raistrick, *loc. cit.*), so that the relative stability of puberulic acid, a dihydroxytropolone derivative, towards potassium hydroxide is not unexpected.

Perhaps the most interesting aspect of the structure (II) for puberulic acid is the manner in which it explains the relationship between puberulic and puberulonic acids. We have shown (*loc. cit.*) that puberulonic acid, on being heated with dilute sulphuric acid under reflux, is converted into puberulic acid with evolution of carbon dioxide: $C_8H_4O_7 + H_2O \longrightarrow C_8H_6O_6 + CO_2$. It is now found that this change occurs even on heating the acid with water at 100° and thus there is a strong suggestion of the presence of a potential β-keto-acid structure in puberulonic acid. We have also previously demonstrated the existence of α-diketone and lactone groupings and we now propose structure (VI) for puberulonic acid in order to accommodate all these features:


(VI.)


(VII.)


(VIII.)

It will be evident that hydrolysis of the lactone group in (VI) gives a β-keto-acid which, on loss of carbon dioxide, passes into a ketonic form of puberulic acid. Structure (VI) also accounts for the α-diketonic properties of puberulonic acid and hence its yellow colour, as well as for the fact that it cannot be acetylated.

Other possible formulæ for puberulonic acid are (VII) and (VIII), if we exclude structures containing a double bond at a bridgehead. Structure (VII) contains a γ-lactone grouping and there is no decisive evidence available at present to distinguish between it and (VI). Whereas the ready opening of the lactone ring on heating the acid with water and the fact that the quinoxaline derivative of puberulonic acid does not evolve carbon dioxide when heated with dilute aqueous methanolic hydrochloric acid tend to favour the δ-lactone structure, the recovery of puberulonic acid on acidification of a solution of the sodium salt is perhaps more indicative of a γ-lactone formula.

The 1 : 2 : 3-triketone structure (VIII) is perhaps less likely, since such a compound would be expected to exist in a hydrated form and exhibit strong reducing properties. Further work is necessary, however, to decide between structures (VI) and (VII).

EXPERIMENTAL.

Conversion of Puberulonic Acid into Puberulic Acid.—A continuous stream of nitrogen, freed from carbon dioxide and oxygen, was passed through a boiling suspension of puberulonic acid (224 mg.) in water (25 c.c.). The carbon dioxide evolved in the reaction was collected quantitatively in barium hydroxide solution (98·8 c.c. of 0·1923N.), and at the end of 8 hours the excess of barium hydroxide was determined by titration (volume of barium hydroxide neutralised by carbon dioxide, 9·5 c.c.; calc. for 1 molar equivalent of carbon dioxide, 10·4 c.c.). The yellow crystalline solid (170 mg.) formed in the course of the reaction was separated and mixed with a further small quantity of solid obtained by continuous extraction of the filtrate for 8 hours. The crude mixture, m. p. 308°, was recrystallised from methanol to give a faintly yellow micro-crystalline powder, m. p. 311°, alone or mixed with an authentic specimen of puberulic acid.

Fusion of Puberulic Acid with Potassium Hydroxide.—Puberulic acid (200 mg.), water (0·5 c.c.), and potassium hydroxide (1 g.) were heated in a salt-bath at 240° and a further quantity of potassium hydroxide (1 g.) was added to increase the fluidity. The bath temperature was slowly raised to 300°, the melt remaining yellow and frothing considerably. After 10 minutes at 300—320°, the melt was cooled, dissolved in water (8 c.c.), and acidified with 3N-hydrochloric acid (12 c.c.) which caused vigorous evolution of gas. The copious precipitate was allowed to settle at 0° overnight, then separated, and dried (117 mg.), m. p. 300°. Mixed with an authentic specimen of puberulic acid, the product had m. p. 310°. The ferric chloride reaction of the material was identical with that of puberulic acid. The filtrate was evaporated to dryness at 50°/13 mm., and the solid residue remaining was continuously extracted with dry ether. Evaporation of the ether failed to yield any residue.

Repetition of the above experiment at a higher temperature, 320—340°, for 20 minutes caused extensive charring and yielded on acidification a deep reddish-brown mass that had m. p. >350° and was not identified.

Oxidation of Puberulic Acid with Hydrogen Peroxide.—Puberulic acid (560 mg.) was dissolved in N-sodium hydroxide (11 c.c.), hydrogen peroxide (4·9 c.c. of 31%) added, and the mixture set aside for 72 hours at room temperature, whereupon the solution changed from orange-red to colourless. The colourless solution was acidified with N-hydrochloric acid (12 c.c.) (evolution of carbon dioxide), and the mixture evaporated at 50°/13 mm. The colourless, rather gummy residue was continuously extracted with dry ether for 9 hours and gave, after removal of the ether *in vacuo*, a white solid contaminated with a trace of colourless resin. Purification was effected by repeated recrystallisation from dry ether-light petroleum (b. p. 40—60°) and finally by recrystallisation from 2N-hydrochloric acid. The purified product formed small white prisms, m. p. 187—189° (decomp.), which had m. p. 186—187° (decomp.) when mixed with authentic aconitic acid (m. p. 186—187°) (Found: C, 41·8; H, 3·5%; equiv. (titration), 59·4, 56. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·5%; equiv., 58).

The above degradation product gave, under the conditions of the fluorescein reaction with resorcinol-sulphuric acid, a red solution with a pale greenish-yellow fluorescence in daylight and a beautiful sky-blue fluorescence in ultra-violet light, identical with that observed using authentic aconitic acid. With pyridine and acetic anhydride it showed the same series of colour changes as authentic aconitic acid.

Reduction of the Hydrogen Peroxide Oxidation Product.—The hydrogen peroxide oxidation product (116 mg.) was dissolved in methanol (25 c.c.) and hydrogenated at atmospheric pressure using Adams's platinum oxide catalyst. The hydrogen uptake was slightly in excess of that calculated for one double bond and was complete in 1 hour. The methanol was removed *in vacuo*, leaving an oil which solidified when kept for 24 hours at 0°. Recrystallisation from acetone (charcoal) yielded tricarballylic acid (50 mg.), m. p. 157—158°; mixed with authentic tricarballylic acid (m. p. 162—163°) it had m. p. 158—160°. Confirmation of the identity was provided by the fluorescein test: the colour observed corresponded precisely with that shown by an authentic specimen.

Nitric Acid Oxidation of Puberulic Acid.—Puberulic acid (50 mg.) was heated with distilled nitric acid (2 c.c.) at 100° for 2 hours. Copious brown fumes were evolved and the mixture rapidly changed from red to pale brown. It was evaporated to dryness at 100°, and water (2 c.c.) added to the residue, which was again taken to dryness. This process was repeated three times, the last trace of volatile material being removed *in vacuo*, leaving a colourless solid residue (20 mg.). This residue gave no colour reaction with ferric chloride but a blue colour with diphenylamine, and decolorised potassium permanganate when gently warmed. Purification was effected by sublimation at 80—90°/2×10^{-2} mm. and yielded oxalic acid (16·7 mg.), m. p. 187—188°, showing no depression on admixture with an authentic specimen of oxalic acid.

Ozonolysis of Puberulic Acid.—Ozonized oxygen was passed through a suspension of puberulic acid (198 mg.) in water (50 c.c.) and then through standard barium hydroxide until dissolution of the acid was complete (3 days). Carbon dioxide equivalent to 5·2 mols. per mol. of puberulic acid was evolved. The titratable acidity of the clear solution was initially 20 c.c. of 0·1N-alkali and decreased to 7·15 c.c. of 0·1N-alkali after ozonization. Steam-distillation of the residue showed that none of the titratable acidity was due to volatile acids, nor did the distillate give any reaction with Brady's reagent. Evaporation of the ozonized solution gave a small amount of an acidic gum (10 mg.) which gave no characteristic colour reactions and was not further investigated.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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3. *Ketonic Products of the Oxidation of the* cis- *and* trans-*Forms of Ricinoleic Acid.*

(Considered in relation with the author's work on the autoxidation of the unsaturated fatty acids.)

By GEORGE W. ELLIS.

The hitherto unknown cis-11-*ketoheptadec*-8-*ene*-1-*carboxylic acid* (λ-*keto-oleic acid*) and its trans-*isomer* (λ-*ketoelaidic acid*) have been prepared by the chromic acid oxidation of ricinoleic and ricinelaidic acid, respectively. Both of these acids containing βγ-olefinic ketone grouping have been transformed, through their common hydrogen bromide additive product, 9-*bromo*-11-*ketoheptadecane*-1-*carboxylic acid* (ι-*bromo*-λ-*ketostearic acid*), into the *trans*-form of their αβ-isomer, trans-11-*ketoheptadec*-9-*ene*-1-*carboxylic acid.* Some of the properties of these compounds have been studied, particularly the quantitative nature of their alkaline hydrolyses. Their reactions with semicarbazide have been studied and special interest attaches to formation, from λ-keto-oleic acid, of a peroxide simultaneously with an *epoxy*-derivative.

THE main purpose of these investigations was to throw further light on the formation of unsaturated ketone groups during the autoxidation of the mono-unsaturated fatty acids. The products obtained from oleic and elaidic acid, after an oxygen uptake at 60—70° of about 20% by weight, contained only a low concentration of these unsaturated keto-acids, but contained substances regarded as resulting therefrom, such as elaidic acid oxide (m. p. 55·5°) in nearly 40% yield with its monoacyl derivatives, and oily, resinous polymers. The amount of these substances became inappreciable when it was found possible to bring about autoxidation at 45—50°. In their place appeared η- and κ-keto-oleic acids, or their *trans*-isomers, as the main autoxidation products (Ellis, *Biochem. J.*, 1936, **30**, 753; 1950, in the press).

The existence of different isomers of these keto-acids and the appreciable chain degradation found to accompany autoxidation led to the formation of a complex mixture of these bodies from which no pure product can, with certainty, be regarded as having been isolated. The present study of similar compounds, obtained in a pure form from ricinoleic and ricinelaidic acids, confirms the evidence for the presence of the unsaturated ketonic acids as significant autoxidation products of the mono-unsaturated fatty acids; similar ketone formation has been observed for 1-methyl*cyclo*hexene (Dupont, *Bull. Soc. chim. Belg.*, 1936, **45**, 57; 1937, **46**, 21; Cook, *J.*, 1938, 1778). It was realised that carefully controlled oxidation of ricinoleic and ricinelaidic acids should afford acids containing $\beta\gamma$-unsaturated ketone groupings in *cis*- and *trans*-forms which by the catalytic action of acids and alkalis might undergo tautomeric change to the respective $\alpha\beta$-forms (cf. Kon *et al.*, *J.*, 1923, 1361 etc.; 1926, 2128). However, the *trans*-$\alpha\beta$-form was obtained from both the *cis*- and the *trans*-$\beta\gamma$-form by way of the hydrobromic acid additive product of the latter (cf. Blaise, *Bull. Soc. chim.*, 1905, **33**, 40).

λ-*Keto-oleic*, m. p. 39°, and -*elaidic acid*, m. p. 73°, have now been prepared by the oxidation of ricinoleic and ricinelaidic acid, respectively, with chromic acid below 15°. Both keto-acids have iodine values lower than the theoretical and, although the latter acid is perfectly stable, the former rapidly autoxidises in air, even at 0°. At room temperatures λ-keto-oleic acid absorbs 3—4 atoms of oxygen with evolution of carbon dioxide, to form a semi-solid mass containing up to 12·5% of a peroxide (calculated as a peroxide of keto-oleic acid with one active oxygen atom), an appreciable proportion of λ-*ketoepoxystearic acid*, m. p. 112·5° (2 : 4-*dinitrophenylhydrazone*, m. p. 119°), and oily substances giving reactions pointing to β-keto-acid formation. The instability of the unsaturated ketones has usually been attributed to polymerisation rather than to autoxidation, but explosive products have sometimes been observed (Eccott and Linstead, *J.*, 1930, 905), suggestive of the peroxide formation observed in the present studies.

In the present study of the autoxidation of oleic and elaidic acid, small and not greatly varying amounts of peroxides were formed at temperatures between 45° and 100°. At the lower temperatures high yields of the unsaturated keto-acids were obtained, with little evidence of their decomposition into the coloured, resinous oils which form the greater part of the products at higher temperatures. At all temperatures within the range, elaidic acid oxide, m. p. 55·5°, was also formed from both oleic and elaidic acid (maximum yield at 60—70°), with a copious evolution of carbon dioxide and water. Some of the oily fractions isolated gave marked enol reactions and yielded carbon dioxide on hydrolysis, so that β-keto-acid formation is probable. The products are thus closely comparable with those obtained by autoxidation of the olefinic keto-acid studied in the course of this work, and since, for the autoxidation of oleic and elaidic acid, a preliminary formation of olefinic keto-acids has been demonstrated in the author's contemporary work (Ellis, 1950, *loc. cit.*), it seems likely that for this process there is a sequence: olefinic acid $\longrightarrow$ olefinic keto-acid $\longrightarrow$ olefinic keto-acid peroxide $\longrightarrow$ peroxidation products, including an epoxide, carbon dioxide, and water with other chain-peroxidation products.

λ-Keto-oleic and -elaidic acid absorb hydrogen bromide in dry carbon tetrachloride solution (cf. Blaise, *Bull. Soc. chim.*, 1905, **33**, 40: Eccott and Linstead, *loc. cit.*) to form the same ι-*bromo*-λ-*ketostearic acid*, m. p. 68°, in good yield. This is converted by aqueous potassium hydrogen carbonate at 100° into 11-*ketoheptadec*-9-*ene*-1-*carboxylic acid*, m. p. 50°, containing an $\alpha\beta$-unsaturated keto-group and considered to be the *trans*-form by analogy with the findings of the authors mentioned above.

Alkaline hydrolysis of λ-keto-oleic and -elaidic acid afforded a 40% yield (theory 43%) of hexyl methyl ketone, the isolation of which was facilitated by the use of a simple still-head (Ellis, 1950, *loc. cit.*). The other hydrolysis product, the semialdehyde of sebacic acid, was not isolated: it appeared to have polymerised under the action of the alkali. Since methyl hexyl ketone was obtained in very similar yields by alkaline hydrolysis of both the *cis*- and the *trans*-form of the $\beta\gamma$-isomers and from the *trans*-form of the $\alpha\beta$-isomer, it seems probable that the first two acids isomerise under the influence of alkalis (cf., *e.g.*, Eccott and Linstead, *loc. cit.*).

Condensed with phenylhydrazine and then treated with sulphuric–nitrous acid, all these olefine-ketonic acids gave an intense purple pyrazoline dye. This reaction was previously regarded as specific for $\alpha\beta$-olefinic ketones. It is a marked reaction of the oily products obtained by the autoxidation of the mono-unsaturated fatty acids and is given by a linseed oil film which has been exposed to the air for a few hours at room temperatures.

EXPERIMENTAL.

λ-*Keto-oleic* (cis-11-*Ketoheptadec*-8-*ene*-1-*carboxylic*) *Acid from Ricinoleic Acid.*—A solution of recently prepared ricinoleic acid (60 g.) in acetic acid (500 ml.) was cooled with occasional stirring so as to crystallise a large proportion of the acetic acid without causing the mass to set and so hinder the next operation. Chromium trioxide (14 g.) in a minimum of water and acetic acid (100 ml.) was added with vigorous stirring, and the mixture was set aside for 2 hours at room temperature. It was then mixed with half its bulk of powdered ice, and the solid product was allowed to separate over a clear lower layer. The solid (which should contain a large proportion of ice) was washed by suction with ice-cold water until colourless. It crystallised from 80% ethanol at 0° in long, thin plates (10 g.), m. p. 39° (Found: C, 72·9; H, 10·7%; I.V., 56. $C_{18}H_{32}O_3$ requires C, 72·9; H, 10·9%; I.V., 85·7).

λ-*Keto-oleic acid* is very soluble in all the common organic solvents and crystallises well from light petroleum. Filtration of its solution in this solvent serves to remove possible traces of the epoxide described below. This acid is very unstable in air, absorbing oxygen to form a peroxide and other substances (see below). Although it clearly reacts with semicarbazide and with 2 : 4-dinitrophenylhydrazine, no pure derivatives have been isolated. It gives the following sensitive test: About 1 mg. is heated for a few seconds with an equal bulk of phenylhydrazine on a slide and the cold product is rubbed into a smear with a small drop of sulphuric acid. A few crystals of sodium nitrite are allowed to react completely with a drop of sulphuric acid. On causing these two smears to run together, an intense bluish-violet mass is obtained.

When boiled with water or diluted sulphuric acid, or when heated alone at 100° for an hour, λ-keto-oleic acid gives a yellow oil.

Alkaline Hydrolysis of λ-*Keto-oleic Acid.*—Slow distillation of this acid with 0·03N-sodium hydroxide in the apparatus referred to above, gave a 40% yield of methyl hexyl ketone (semicarbazone, m. p. and mixed m. p. 121°), but the yields fell off with an increased concentration of alkali:

Wt. taken, g.	Alkali.	Methyl hexyl ketone, g.	Yield, %.	Yield, %, corr.
0·2689	0·03N-NaOH	0·0960	36	40
0·1738	0·05N-NaOH	0·0535	31	34
0·2087	N-NaOH	0·0500	24	26
0·1510	10% KOH	0·0325	22	24
0·1958	10% K_2CO_3	0·0407	21	23

A blank experiment with pure methyl hexyl ketone in the same apparatus gave a 90% recovery, and the yields have been corrected accordingly, as shown in the last column. With the more concentrated alkali the hydrolytic reaction appears to be replaced in part by polymerisation. Acidification of the products remaining after distillation of the methyl hexyl ketone resulting from the less concentrated alkaline hydrolyses gave, apparently, polymers of sebacic acid semialdehyde as semi-solid oils [Found: equiv., 186. Calc. for $(C_{10}H_{18}O_3)_n$: equiv., 186]. This equivalent rose to 240—260 when more concentrated alkali was employed, furnishing some evidence that the lower yield of methyl hexyl ketone was caused by polymerisation of the olefinic keto-acid. No Schiff's or other aldehydic reaction could be obtained, either before or after boiling these oils with dilute sulphuric acid, nor could any sebacic acid be detected after their oxidation with potassium permanganate. In such respects these sticky oils bear a close analogy with the polymerised product which King (*J.*, 1938, 1826) obtained by the action of alkali on azelaic acid semialdehyde.

λ-*Keto-elaidic* (trans-11-*Ketoheptadec*-8-*ene*-1-*carboxylic*) *Acid.*—Ricinelaidic acid, m. p. 52°, was prepared by exposing a layer of ricinoleic acid to nitrous fumes for about 2 days and purifying the product with dilute ethanol. This was oxidised with chromic acid in acetic acid in the manner described above. The crude product, however, was crystallised from 90% ethanol at room temperatures, unchanged ricinelaidic acid being retained in the mother-liquors. λ-*Keto-elaidic acid* (30%) crystallised from ethanol in rhombic and hexagonal plates, m. p. 73° (Found: C, 72·9; H, 10·8%; I.V., 68), and gave a *semicarbazone*, m. p. 94° (Found: N, 12·0. $C_{19}H_{35}O_3N_3$ requires N, 11·9%). The keto-acid was stable in air (during some months) and gave the pyrazoline test. It also gave a reddish-orange colour when treated with the phenylhydrazine and sulphuric acid alone. It was much more stable towards heat than was the *cis*-isomer, suffering only slight change during 2 hours at 100°, and afforded, though more slowly than its isomer, a 41% yield of methyl hexyl ketone on hydrolysis with 0·05N-sodium hydroxide.

9-*Bromo*-11-*ketoheptadecane*-1-*carboxylic Acid.*—λ-Keto-oleic (or elaidic) acid (1 g.) in carbon tetrachloride (10 ml.) was saturated with hydrogen bromide and the corked vessel was left in a cool place. The 9-*bromo*-11-*ketoheptadecane*-1-*carboxylic acid* which separated was crystallised from a filtered, light petroleum solution and then from carbon tetrachloride or 90% ethanol. It formed rods with pointed ends, often appearing as plate-like bundles (1·1 g.), m. p. 68° (Found: C, 57·2; H, 8·6; Br, 22·2. $C_{18}H_{33}O_3Br$ requires C, 57·3; H, 8·8; Br, 21·2%).

trans-11-*Ketoheptadec*-9-*ene*-1-*carboxylic Acid.*—The bromo-keto-acid was heated for 2 hours at 100° with 10% aqueous potassium hydrogen carbonate. After acidification the solution was extracted with light petroleum, and the residue left on evaporation of the solvent was crystallised successively from carbon tetrachloride (norite) and from ethanol. trans-11-*Ketoheptadec*-9-*ene*-1-*carboxylic acid* crystallised in well-defined hexagonal plates, m. p. 50° (Found: equiv., 297; I.V., 24. $C_{18}H_{32}O_3$ requires equiv., 296; I.V., 85·7). A low iodine value has been observed for αβ-olefinic ketones (Eccott and Linstead, *loc. cit.*). The acid gave a marked pyrazoline colour reaction, and with sulphurous acid gave a stable oil. Hydrolysis of the acid with 0·05N-sodium hydroxide gave a 32·5% yield of methyl hexyl ketone. Autoxidation of this $\alpha\beta$-isomer is under investigation.

Autoxidation of λ-*Keto-oleic Acid*.—(*a*) Specimens of λ-keto-oleic acid, left in loosely corked tubes for several months, became sticky and did not melt completely below 100°. The peroxide values ranged from 4·3 to 12·5% (calc. as a peroxide of the original acid). Extraction of the tube contents with light petroleum gave an unstable oily product of 17% peroxide content, which resisted further purification. The solid left after the extraction with light petroleum was extracted with acetone, and the solution filtered and evaporated. The residue in ethanol yielded an epoxide in the form of well-defined hexgonal plates of λ-*ketoepoxystearic* (11-*keto*-8 : 9-*epoxyheptadecane*-1-*carboxylic*) *acid*, m. p. 112·5° [Found : C, 69·1; H, 10·1; equiv., 311; *M* (Rast), 336; I.V., 5. $C_{18}H_{32}O_4$ requires C, 69·2; H, 10·3%; equiv. = *M*, 312]. The 2 : 4-*dinitrophenylhydrazone* crystallised in plates, m. p. 119° (Found : N, 11·0. $C_{24}H_{36}O_7N_4$ requires N, 11·4%). Attempts to prepare a semicarbazone yielded an impure, yellow, amorphous *substance*, m. p. 201°, nearly insoluble in ethanol (Found : N, 18·2. $C_{19}H_{35}O_4N_3$ requires N, 11·4%).

This keto-epoxy-acid was also isolated in small amount as a by-product in the preparation of λ-keto-elaidic acid described above, and was detected in smaller amounts in the mother-liquors from λ-keto-oleic acid preparations. It was isolated by means of its sparing solubility in lukewarm light petroleum. When prepared from these sources this compound may have acquired its epoxy-group by autoxidation of the ricinoleic acid used for the chromic acid oxidations.

(*b*) λ-Keto-oleic acid (0·0576 g.) was dispersed on a small, opened roll of filter paper (36 sq. cm.), placed in the upper part of a test-tube containing a little saturated aqueous barium hydroxide at the base. The air was replaced by oxygen and the tube connected with a manometer and a source of oxygen. After 55 days, at room temperatures, 6·84 ml. (17% by wt.) of oxygen had been absorbed, corresponding to the addition of 3·33 atoms of oxygen. Acidification of the alkaline solution gave 0·49 ml. of carbon dioxide. The ratio of oxygen evolved as carbon dioxide to the total oxygen uptake was 0·07 as compared with ratios of 0·2—0·4 found for the autoxidation of monounsaturated fatty acids (Ellis, *loc. cit.*).

Extraction of the main autoxidation products from the filter paper with peroxide-free ether furnished a semi-solid material containing crystals of the λ-ketoepoxystearic acid and 15% of peroxide.

(*c*) λ-Keto-oleic acid was autoxidised in air in the form of a thin film on a glass plate at 42°. After 24 hours, extraction with *n*-hexane gave an oil containing 27% of peroxide. A solid fraction, insoluble in the cold solvent, was identified as the ketoepoxystearic acid.

The oily products of the above autoxidations gave enol reactions, which were not given by any of the olefinic keto-acids. These oils also yielded small quantities of sodium carbonate when hydrolysed by sodium hydroxide. The presence of β-keto-acids in these autoxidation products was therefore indicated.

Pyrazoline Test.—The purple colour obtained in the tests described above was also given by the oils from the autoxidation of the monounsaturated fatty acids and by linseed oil which had been exposed to the air for a day, or for a few hours in warm weather. A film of linseed oil so treated gives with concentrated sulphuric acid a deep brown colour, masking the bluish-purple colour of the test, which was, therefore, slightly modified in this case. The autoxidised film (about 1 mg.) was mixed with phenylhydrazine (about 2 mg.). The application of very little heat sufficed to bring about a vigorous reaction. The resulting mass was taken up in a few drops of chloroform and the solution dropped on the sulphuric and nitrous acid mixture. Intense blue or purple colours were obtained in this way.

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ST. MARY'S HOSPITAL MEDICAL SCHOOL, LONDON, W.2. [*Received, June 21st*, 1949.]

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4. *The Seed Fat of* Parinarium laurinum. *Part I. Component Acids of the Seed Fat.*

By J. P. RILEY.

The component acids of the seed oil of *Parinarium laurinum* have been examined and shown to contain besides parinaric acid, reported by earlier workers, substantial amounts of α-elaeostearic and oleic acids, together with minor proportions of palmitic, stearic, linoleic, and conjugated octadecadienoic acids. The identities of the unsaturated acids have been established by oxidation or bromination. Spectrographic values are presented for the determination of parinaric acid in oils, and for its behaviour to alkali isomerisation under the conditions used for the analysis of oils containing α-elaeostearic and linoleic acids. The mean composition of the component mixed fatty acids of two samples of oil from seeds collected in the Fiji Islands has been shown by low temperature crystallisation and spectrographic methods to be : palmitic 4, stearic 1, oleic 7·5, linoleic 2, conjugated octadecadienoic 1·5, α-elaeostearic 30·5, and parinaric acid 53·5% (wt.).

PARINARIUM LAURINUM, belonging to the family Rosaceæ, is a tree of moderate size, about 3 feet in girth and 30 feet high. It grows in Papua and New Guinea, Java, Borneo, and prolifically on the sea front and river valleys of the Fiji Islands. The tree bears ovoid fruit resembling potatoes and varying considerably in size; these are greatly valued by the natives for medicinal and other purposes, and are known by a number of native names, the principal of which are Makita (Fiji) and Kusta (New Guinea).

The fruit itself consists of a light-brown, very fibrous shell about ¼" thick, containing a moist, pink kernel. Farmer and Sunderland (*J.*, 1935, 759) found 44% of oil in the kernels. In a private communication Mr. G. Winter writes : " We had obtained a parcel of seeds from New Guinea, which contained seeds which had been collected in various areas of the territory. Examining individual seeds we found the oil content to vary from 3% to 40% of the kernel, the majority being between 20% and 35%. There was also great difference between individual seeds in the shell : kernel ratio. So far, we have not been able to distinguish between high and low oil-bearing seeds according to general appearance, size, or shape. According to Mr. Parham of the Department of Agriculture, Fiji, four varieties of *Parinarium laurinum* are known, all of which bear similar fruit, but differ in the shape of the leaves." The properties of the oil and its actual and possible uses have been discussed in two recent reviews (Anon., *Paint Manuf.*, 1945, **15**, 356; Winter, Nunn, and Ward, *Paint Notes, Austral.*, 1948, **3**, 393).

The chemical composition of the component acids of the oil was first examined by Tsujimoto and Koyanagi (*J. Soc. Chem. Ind. Japan*, 1933, **36**, 110, 673), who crystallised the mixed fatty acids from light petroleum and isolated an acid of melting point 85—86°, which they named parinaric acid but considered to be a geometrical isomer of elaeostearic acid. The same acid was also isolated by Farmer and Sunderland (*loc. cit.*) in 24% yield from the mixed fatty acids of the oil. These workers were able to show that, on hydrogenation, parinaric acid absorbed 4 molecules of hydrogen, yielding stearic acid. Oxidation by alkaline permanganate yielded azelaic, propionic, and oxalic acids, they therefore concluded that parinaric acid is octadeca-9 : 11 : 13 : 15-tetraenoic acid.[*] These findings were later supported by Kaufmann, Baltes, and Funke (*Fette u. Seifen*, 1938, **45**, 302), who showed that the ultra-violet absorption spectrum of parinaric acid was very similar to that of decatetraene and concluded that the acid contains four conjugated double bonds.

More recently the absorption spectrum of the mixed fatty acids from the oil has been examined by Winter (*Paint Notes, Austral.*, 1948, **3**, 393) who concluded that, besides parinaric acid (46%), there was also present about 34% of a conjugated trienoic acid—probably α-elaeostearic acid.

The present part of this work has as its aims the identification of the component fatty acids present in the oil, and their determination. Three samples of oil have been studied, two of which were extracted in Australia by Winter, and a third which was extracted in Liverpool from seeds collected near Suva. In Table I are given the physical constants of the oils, together with those reported by other workers.

TABLE I.

Sample.	I.	II.	III.	IV.	V.
% of oil in dry kernels	12·9	12	—	—	17·6
n^{40}	1·5510	1·5527	1·5480	1·5610 [b]	1·5610 [c]
Free fatty acid (as oleic), %	18·8	—	2·8	0·6	5·9
I val.	180·8 [a]	179·0 [a]	176·8 [a]	214·4	185 [d]
I val. (Toms)	240·3	255·8	229·3	—	—
Unsaponifiable matter, %	—	1·0	0·9	1·15	0·9

[a] 20 c.c. of Wijs reagent (200% excess) on 0·1 g. of fat; reaction period, 30 minutes.
[b] At 50°. [c] At 15°. [d] Wijs reagent (200% excess) for 1 hr. at 20°.

I. Seeds collected near Suva and extracted in Liverpool.
II. Oil extracted in Australia from seeds collected near Suva (Fiji).
III. Oil extracted in Australia from seeds collected in Fiji.
IV. Tsujimoto and Koyonagi (*loc. cit.*).
V. Winter's (*loc. cit.*) seed collected near Suva.

There thus seems to be reasonable agreement between the values recorded by the various workers, for all the constants, except the free acidity and iodine values. The free acidity depends greatly on the maturity of the seeds, and their method of collection and storage, and the iodine value varies, when unsaturated acids having conjugated double bonds are present, with the reagent used, its excess, and the time of reaction.

Pure parinaric acid, m. p. 86°, has been isolated by repeated crystallisation of the mixed fatty acids from light petroleum and ether. The acid has been subjected to acetone-permanganate oxidation, yielding azelaic acid as the sole dibasic acid, which confirms the structure for the acid proposed by Farmer and Sunderland (*loc. cit.*). The ultra-violet absorption spectrum of the acid (Fig. 1.) agreed fairly well with the observations of Kaufmann *et al.* (*loc. cit.*) and Winter (*loc. cit.*) (see Table II).

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[*] In this paper numbering is according to the Geneva system, the number 1 being assigned to CO_2H.

TABLE II.

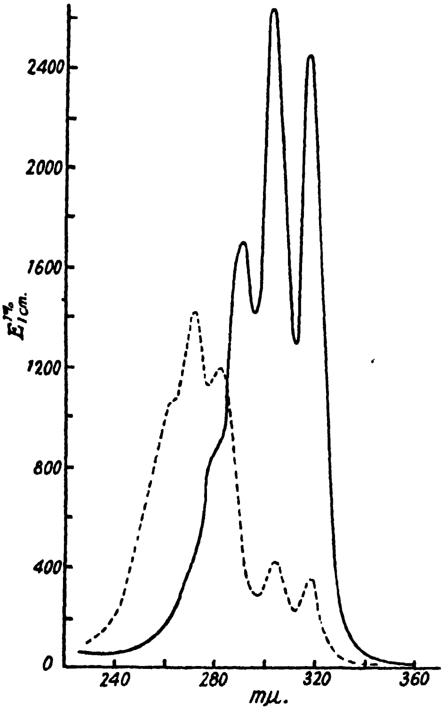
Absorption spectrum of parinaric acid.

	$\lambda_{max.}$ at mμ.	$E^{1\%}_{1\,cm.}$.	$\lambda_{max.}$ at mμ.	$E^{1\%}_{1\,cm.}$.	$\lambda_{max.}$ at mμ.	$E^{1\%}_{1\,cm.}$.
Present work	291·5	1694	305	2624	320	2450
Kaufmann *et al.* (*loc. cit.*) ...	—	—	307	—	—	—
Kaufmann & Keller[1]	292·5	1906	306·5	2800	321·5	2400
Winter (*loc. cit.*)	293	1820	305	2800	319	2500

[1] *Ber.*, 1948, **81**, 152 (in heptane).

The isolation, in a pure state, of the triene acid present in the mixed fatty acids has not proved possible, either by crystallisation or by chromatographic adsorption on silica gel. The difficulty of separation is largely due to the extremely labile nature of the parinaric and triene acids, and partly to the comparatively small difference in solubility. Nevertheless a concentrate containing 76% of conjugated triene with 16% of parinaric acid has been obtained by crystallisation. This acid shows an absorption spectrum having maxima at the same wavelengths as α-elaeostearic acid (Fig. 1). The methyl ester of the concentrate on oxidation by means of permanganate in acetone yielded azelaic acid as the sole dibasic acid in amount considerably greater than would have been yielded by the parinaric acid present. The triene acid must therefore have its double bonds in the 9 : 11 : 13-positions, and thus be either α-elaeostearic acid or a *cis-trans*-isomer thereof. Its identity as α-elaeostearic acid has been proved by its conversion into its maleic anhydride adduct, which after crystallisation from light petroleum had melting point 62°, and did not depress the melting point (62—63°) of an authentic specimen. The absorption spectra of the two maleic anhydride adducts were identical (Fig. 2). Parinaric acid, when treated with maleic anhydride under the same conditions, yielded only a brownish resin, insoluble in light petroleum.

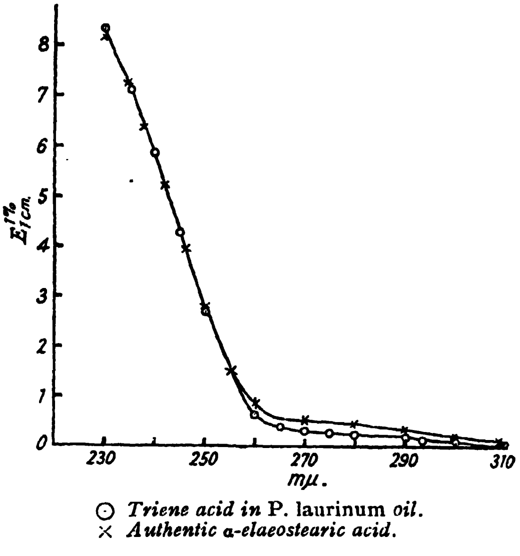
FIG. 1.



Absorption spectra of pure parinaric acid, continuous line. Concentrate of trienoic acid, broken line.

FIG. 2.

Absorption spectra of maleic anhydride adducts.



A small amount of conjugated dienoic acid also occurs in the mixed acids, as shown by a maximum in the absorption curve at 234 mμ. It has not been possible to obtain a sufficiently high concentration of the acid for it to be identified, but by analogy it is probably octadeca-9 : 11-dienoic acid. The spectrum of the mixed acids has been examined without success for the presence of conjugated pentaenoic or more unsaturated acids.

The non-conjugated unsaturated acids present have been shown by conversion into di- and tetra-hydroxystearic acids (by oxidation of concentrates of the acids with dilute alkaline permanganate) to be the normal oleic and linoleic acids occurring in seed oils. On bromination of the concentrate in ether, no insoluble hexabromides were obtained, agreeing with the findings of Hilditch and Riley (*J. Soc. Chem. Ind.*, **1946**, **65**, 74T) that linolenic acid does not occur in the presence of α-elaeostearic acid.

The principal saturated acid present in the oil has been shown—after hydrogenation and fractionation of the methyl esters of the mixed acids—to be palmitic acid. Small amounts of lower saturated acids also occur in the oil; these have not been identified, but are probably oxidation products of the parinaric acid.

The compositions of the mixed acids from two of the samples of oil have been determined by a modification of the methods used by Hilditch and Riley (*loc. cit.*) for the examination of oils containing elaeostearic acid. The mixed acids were resolved into fractions by crystallisation from light petroleum and acetone at low temperatures, before spectroscopic examination. The parinaric acid was determined by the absorption of the alcoholic solution at 305 mμ. After allowance has been made for its absorption at 270 mμ. (band-head of α-elaeostearic acid) and at 234 mμ. (band-head of conjugated diene), the elaeostearic and conjugated dienoic acids were determined. Similar corrections were applied to the values obtained by alkali isomerisation for the determination of linoleic and linolenic acid. Values used in the calculations, determined with pure parinaric acid, are given in Table III (values used in the calculation of results are given in bold type).

TABLE III.

$E^{1\%}_{1\,\text{cm.}}$ for pure parinaric acid.

$E^{1\%}_{1\,\text{cm.}}$ at	234 mμ.	270 mμ.	291·5 mμ.	305 mμ.	320 mμ.
Untreated	**53·6**	**386**	1694	**2624**	2450
Alkali-treated, 170°/15 mins.	90·6	**452**	—	—	—
Alkali-treated, 180°/60 mins.	**91·0**	—	681	744	473

Saturated acids were determined in each case by the Bertram method (*Z. deutsch Oel Fett Ind.*, **1925**, **45**, 733) and palmitic acid by fractionation of the hydrogenated methyl esters as proposed by Gunstone and Hilditch (*J. Soc. Chem. Ind.*, 1946, **65**, 8T).

From the data obtained the component fatty acids (excluding unsaponifiable matter) of the two oils have been deduced (see Table IV).

TABLE IV.

Component fatty acids of Parinarium laurinum *(excluding unsaponifiable matter).*

	Sample II (from Suva).	Sample III.
Palmitic + stearic	4	5
Oleic	6	10
Linoleic	2	2
Linolenic	—	—
Conjugated octadecadienoic	1	2
α-Elaeostearic	31	30
Parinaric	56	51

From these figures it will be seen that there is comparatively little difference between the two oils, although the proportion of parinaric acid is rather variable. The analysis confirms the deduction made from bromination, that linolenic acid is absent. It is thus evident that *P. laurinum* is similar to many other members of the *Parinarium* species in containing α-elaeostearic acid, with lesser amounts of linoleic, oleic, and palmitic acid, but is so far as is known almost unique in also containing the conjugated tetraenoic parinaric acid. Parinaric acid has, however, been reported in the seed fats of *P. glaberrimum* and *P. scabium* (Frahm, *De Ingenieur in Nied-Indie*, **1941**, **7**, 42) and of a few members of the Balsaminaceæ, *e.g.*, *Impatiens Roylei Walpers* (Kaufmann and Keller, *loc. cit.*).

Since the completion of this work the following private communication has been received from Mr. Winter: " Some (*P. laurinum*) fats when examined spectrophotometrically were found to contain more trienoic than tetraenoic acid, in others again there was hardly an inflexion at the 271·5-mμ. band and the spectrum showed only the characteristic maxima for the tetraene acid. The unfortunate part, however, is that there appears to be no correlation whatsoever in these differences with the appearance, size, or shape of the seeds."

EXPERIMENTAL.

The following data were obtained on the oil extracted by light petroleum (sample III) in Australia, and similar results were obtained for the oil sample from Suva (sample II).

Characteristics of the Oil.—Iodine value (Wijs, on a 0·1-g. sample for 30 minutes) 176·8, iodine value (Toms) 229·3, free fatty acid (as oleic) 2·8%, unsaponifiable matter [by Society of Public Analysts' method (*Analyst*, 1933, **58**, 203)] 0·9%, n^{40} 1·5480, total saturated acids (Bertram) 5·2%.

Hydrolysis of the Oil and Low-temperature Crystallisation of the Mixed Acids.—The oil (46·9 g.) was neutralised with potassium hydroxide solution, and the neutral oil hydrolysed by boiling it under reflux for an hour with a solution of 25 g. of potassium hydroxide in 250 ml. of alcohol. The acids were liberated from the soaps with sulphuric acid and extracted with ether as rapidly as possible to prevent polymerisation. After removal of the ether the acids were preserved in the dark in a well-corked flask filled with carbon dioxide and stored on solid carbon dioxide until required, to prevent the polymerisation of parinaric acid.

The mixed acids (42·53 g.) from the oil were boiled with 350 ml. of light petroleum, and the solution decanted from the resinous polymerised material P_1, the latter was washed twice with 40 ml. of boiling light petroleum, and the washings added to the main solution. The solution of the acids in light petroleum was crystallised at −25°, and the deposited acids (36·52 g.) were recrystallised from light petroleum (50 ml./g.) at 0°, yielding crystallised acids *A* (22·17 g.), polymerised material P_2 (0·90 g.) (which was combined with P_1; total, 2·62 g.), and soluble acids (13·45 g.). The soluble acids were recrystallised from light petroleum (20 ml./g.) at −35°, giving crystallised acids *B* (12·18 g.) and soluble acids *C* (1·27 g.). The soluble acids (4·29 g.) from the crystallisation from light petroleum (10 ml./g.) at −25° were recrystallised from acetone (10 ml./g.) at −60°, yielding insoluble acids *D* (1·19 g.) and soluble acids *E* (3·10 g.). Data for these fractions are given in Tables V, VI, and VII.

TABLE V.

Crystallisation data.

Fraction.	Wt., g.	%.	I val. (Toms).
A	22·17	52·1	—
B	12·18	28·7	—
C	1·27	3·0	176·2
D	1·19	2·8	—
E	3·10	7·3	196·3
P_1	1·72	4·0	—
P_2	0·90	2·1	—
	42·53		

TABLE VI.

Spectrographic examination of fractions.

	Untreated.				Alkali isomerised	
					at 170° for 15 mins.	at 180° for 60 mins.
Fraction. $E^{1\%}_{1\,\mathrm{cm.}}$ at	234	270	305	320	270	234 mμ.
Mixed acids *	100·5	667	1267	1106	687	120·8
A	97·0	539	1945	1725	569	106·8
B	142·2	1029	612	500	952	151·9
C	155·9	749	283	206	699	223
D	96·4	890	123·0	95·3	835	128·9
E	127·0	635	324	245	615	265

* Including polymerised.

TABLE VII.

Component acids of fractions (% wt.).

	Mixed acids.*	*A*.	*B*.	*C*.	*D*.	*E*.
Saturated Oleic Unsaponifiable	22·5	9·4	21·3	36·1	43·2	35·1
Linoleic	0·7	—	0·9	7·8	3·1	15·3
Linolenic	—	—	—	—	—	—
Conjugated dienoic	1·5	2·3	1·7	5·6	—	4·3
Conjugated trienoic	27·0	14·2	52·8	39·7	49·0	33·0
Parinaric	48·3	74·1	23·3	10·8	4·7	12·3

* Including polymerised.

Determination of Palmitic Acid by Hydrogenation.—The refined oil (53 g.) was hydrogenated at 100° with Raney nickel, and the product [I val. (Wijs), 100·3] was saponified. The acids were converted into the methyl esters, which were rehydrogenated at 100°. The product (I val., 12·1) was fractionated as proposed by Gunstone and Hilditch (*loc. cit.*); 4·2% of palmitic acid were present, together with a quantity of polymerised matter (see Table VIII).

TABLE VIII.

Fractionation of hydrogenated methyl esters of Parinarium laurinum *oil.*

No.	G.	Sap. equiv.	I val.	Palmitic.	C_{18}.
*H*1	1·97	276·1	4·6	1·50	0·47
*H*2	2·80	295·5	1·7	0·23	2·57
*H*3—*H*12	31·85	299·1—326·6	1·8—12·9	—	31·85
Residue	4·97	376·2	66·5	—	4·97
Total	41·59		Total	1·73	39·86
			Palmitic acid, %	4·2	95·8

From the above results, the composition of the mixed acids of the oil was calculated to be as shown in Table IX.

TABLE IX.

Component acids of Parinarium laurinum *seed fat* (%, wt.).

Fraction :	*A.* (52·1%).	*B.* (28·7%).	*C.* (3·0%).	*D.* (2·8%).	*E.* (7·3%).	P_1+P_2. (6·1%).	Total.	Acids including unsaponifiable, % (wt.).
Palmitic	4·90	6·11	1·08	1·21	2·55	—	4·20	4·2
Stearic							1·00	1·0
Unsaponifiable							0·90	—
Oleic							9·75	9·9
Linoleic	—	0·26	0·23	0·09	1·13	—	1·71	1·7
Conj. dienoic	1·20	0·49	0·17	—	0·31	—	2·17	2·2
Conj. trienoic	7·40	15·15	1·19	1·37	2·41	—	27·52	30·1
Parinaric	38·60	6·69	0·33	0·13	0·90	—	46·65	50·9
Polymerised * ...	—	—	—	—	—	6·10	6·10 *	—

* The polymerised acids have been assumed to arise from elaeostearic and parinaric acids in the relative proportions observed for these acids.

Identification of Acids.—Palmitic acid. Fraction *H*1 (1·31 g.; Table VIII) was redistilled through a micro-distillation apparatus, yielding a fraction (0·37 g.) of sap. equiv. 272·9, which was converted into its *p*-bromophenacyl derivative; after recrystallisation from alcohol this had m. p. 82—83·5° alone or mixed with *p*-bromophenacyl palmitate (m. p. 83·5—84°).

Parinaric acid. (i) Crystallisation fraction *A* (Table V) was recrystallised repeatedly from light petroleum and ether, and yielded parinaric acid, m. p. 86°, $E^{1\%}_{1\,\mathrm{cm.}}$ 2624 at 305 mμ.; these values could not be increased by further crystallisation. The above spectrographic value was the mean obtained by triplicate determinations (ranging from 2604 to 2644) on four preparations of parinaric acid.

(ii) *Oxidation of methyl parinarate.* Parinaric acid (7·00 g.) was esterified with methyl alcohol containing 0·5% of hydrogen chloride. The resultant esters (4·91 g.) were oxidised in solution in 100 ml. of acetone with 50 g. of potassium permanganate. There was obtained 1·00 g. of crude dibasic acid, together with a considerable amount of ether-insoluble polymerised material. The acid on recrystallisation from 100 ml. of water yielded 0·31 g. of azelaic acid, m. p. 102—104° alone or mixed with authentic material (m. p. 103—105°). Parinaric acid (17·95 g.) on oxidation under the same conditions yielded 4·63 g. of crude azelaic acid, which on recrystallisation from water had m. p. 103—104°.

(iii) *Combination of parinaric acid with maleic anhydride.* Parinaric acid (2·80 g., 0·01 mol.) was heated to 100° for 5 minutes in an atmosphere of carbon dioxide with maleic anhydride (2·1 g., 0·0215 mol.). The resultant dark viscous fluid, which was insoluble in light petroleum, solidified in 2 days to a hard brittle resin.

α-Elaeostearic acid. (i) *Preparation of a concentrate of the trienoic acid.* The mixed acids (133 g.) from the oil were crystallised from 2660 ml. of light petroleum at 0°. The resultant filtrate was then cooled to −15°, and a further crop of crystals (12·8 g.) removed. The volume of the filtrate was reduced to 800 ml., and the solution cooled to −65°. The deposited crystals (34 g.) were recrystallised from light petroleum (900 ml.) at −45° and then from 300 ml. of ether at −20°. The soluble acids (23·2 g.) from the ether crystallisation were twice crystallised from acetone at −15° and then at −75°. The crystalline product (14·5 g.) had $E^{1\%}_{1\,\mathrm{cm.}}$ 1409 at 270·5 mμ. and 428 at 305 mμ., corresponding with 76·3% of α-elaeostearic and 16·3% of parinaric acid. This concentrate was used for the characterisation of the triene acid.

(ii) *Oxidation of the concentrate.* The methyl ester (5·14 g.) of the concentrate was oxidised in 50 ml. of acetone with 35 g. of potassium permanganate. The crude dibasic acid (1·50 g.) after recrystallisation from 100 ml. of water yielded 0·553 g. of azelaic acid, m. p. 103—105° (mixed m. p. undepressed).

(iii) *Preparation of the maleic anhydride adduct of the trienoic acid.* The concentrate (3·28 g.) was heated with maleic anhydride (0·72 g.) at 105° for 15 minutes in a current of carbon dioxide. The cooled mixture was boiled twice with light petroleum (100 ml.), and the clear liquid decanted from the small amount of insoluble oil. On cooling, there separated from the light petroleum 0·5 g. of a white crystalline adduct, which was twice recrystallised from 140 ml. of light petroleum, yielding 0·38 g. of adduct, m. p. 62—63° (undepressed by the maleic anhydride adduct of α-elaeostearic acid, m. p. 62—63°).

(iv) *Preparation of maleic anhydride addition compound of α-elaeostearic acid.* α-Elaeostearic acid (2·78 g., 0·01 mol.), $E^{1\%}_{1\,\text{cm.}}$ 1795 at 270·5 mμ., was heated with maleic anhydride (1·0 g., 0·0102 mol.) at 105° for 15 minutes. The adduct was separated and recrystallised as above, yielding 0·31 g. of colourless adduct, m. p. 62—63° (Morrell and Samuels, *J.*, 1932, 2251, record m. p. 62·5°). The ultra-violet absorption spectra of this compound and the adduct from the concentrates of the triene acid were identical.

Linoleic and oleic acid. Preparation of a concentrate of linoleic and oleic acid. The mixed acids (210 g.) from the oil were crystallised from 2·5 l. of light petroleum at −70°, and the resultant liquid acids (80·5 g.) were recrystallised from 400 ml. of light petroleum at −60°. The filtrate from this crystallisation [11·9 g.; I val. (Toms), 135·9], which contained linoleic 17·3, parinaric 3·2, α-elaeostearic 15·2, and conjugated dienoic acids 5·5%, was employed for the characterisation of oleic and linoleic acid.

(i) *Bromination* (*detection of linoleic acid*). The concentrate (3·05 g.) was brominated in 60 ml. of light petroleum at −10° with 0·82 ml. of bromine. The clear liquid was decanted from the deposited oil and set aside overnight at 0°. 0·29 G. of crystalline bromides separated. The latter were recrystallised from 10 ml. of ether at −40°, yielding 0·102 g. of 9 : 10 : 12 : 13-tetrabromostearic acid, m. p. 113·5—114° alone or mixed with authentic tetrabromostearic acid, m. p. 114°. Complete solubility of the bromides in ether indicated the absence of hexabromostearic acid, and hence of linolenic acid from the oil.

(ii) *Oxidation with dilute alkaline permanganate.* The concentrate (7·37 g.) was oxidised by the method of Lapworth and Mottram (*J.*, 1925, **127**, 1628). There were recovered 1·63 g. of hydroxy-acids and 2·23 g. of saturated and unoxidised acids. On recrystallisation of the former from water and ethyl acetate, 0·50 g. of dihydroxystearic acid, m. p. 132°, was obtained (mixed m. p. with 9 : 10-dihydroxystearic acid, m. p. 132°, undepressed). In addition the two 9 : 10 : 12 : 13-tetrahydroxystearic acids, m. p. 153° (0·32 g.) and 173° (0·13 g.), formed by the oxidation of linoleic acid, were also recovered.

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DEPARTMENT OF INDUSTRIAL CHEMISTRY,
THE UNIVERSITY, LIVERPOOL.

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5. *Hydrolyses and Derivatives of Some Vesicant Arsenicals.*

By WILLIAM A. WATERS and J. HOWARTH WILLIAMS.

The hydrolyses of pure 2-chlorovinyldichloroarsine (Lewisite-I) and of phenyldichloroarsine have been studied by using the partitions of their solutions between benzene and water. Several dialkyloxy-derivatives of Lewisite-I, and some analogous dithiols, have been made, and it has been found that dithiocarbamates are particularly useful for characterising the arsenical vesicants. Lewisite-I gives a characteristic solid with dioxan, and arsenic trichloride with thioxan.

Hydrolysis of β-Chlorovinyldichloroarsine.—The hydrolysis of Lewisite-I by water involves the following equilibria:

$$\mathrm{ClCH{:}CH{\cdot}AsCl_2 + 2H_2O \overset{(fast)}{\rightleftharpoons} Cl{\cdot}CH{:}CH{\cdot}As(OH)_2 + 2HCl}$$

$$\underset{\text{(I.)}}{\mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2}} \underset{\text{(slow)}}{\rightleftharpoons} \mathrm{H_2O} + \underset{\text{(II.)}}{\mathrm{Cl{\cdot}CH{:}CH{\cdot}AsO}} \underset{\text{(slow)}}{\rightleftharpoons} \underset{\text{(III.)}}{\mathrm{(Cl{\cdot}CH{:}CH{\cdot}AsO)_n}}$$

The only substance which can be isolated is polymerised 2-chlorovinylarsinoxide (III), a white insoluble powder of indefinite m. p. Measurements of the equilibria, however, indicate that both the hydroxide (I) and the unpolymerised oxide (II) must be capable of existence in solution in water and benzene respectively.

On treatment with water, Lewisite-I immediately gives a strongly acid solution and a sticky gum, consisting of unchanged Lewisite and (III). If however Lewisite-I is mixed with benzene and then treated with water two clear liquid layers are obtained which, when shaken, rapidly attain an equilibrium which is independent of the initial concentration of the Lewisite-I in the benzene layer. Both the layers can be analysed for (i) chlorine content, (ii) acidity, and (iii) tervalent arsenic by titration with silver nitrate, alkali, and iodine, respectively, and in this way the equilibria attained in the hydrolysis can be found. Figs. 1 and 2 show the results obtained.

The equilibrium attained on shaking a benzene solution of Lewisite-I with aqueous hydrochloric acid corresponds exactly to that reached on shaking a corresponding amount of Lewisite-I with a proportionately smaller volume of water; that is, the percentage of Lewisite-I which remains as such in the benzene layer depends only on the acidity, the bulk of the aqueous layer being immaterial.

FIG. 1. FIG. 2.

Hydrolysis of Lewisite-I in benzene at 17° in ½ hour.

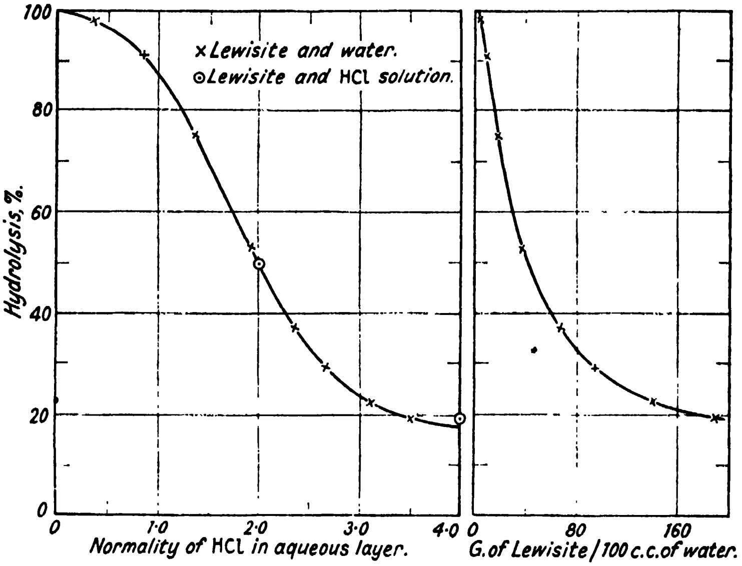
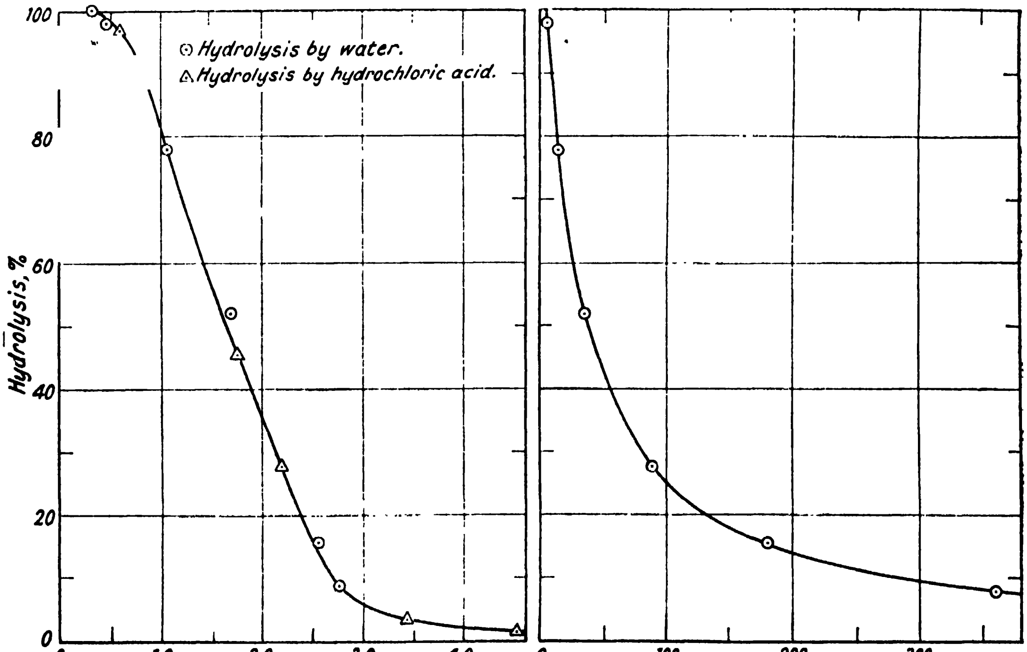


FIG. 3. FIG. 4.

Hydrolysis of phenyldichloroarsine in benzene at 15°.



The hydrolysis of phenyldichloroarsine has been studied in a similar way, giving results which are shown in Figs. 3 and 4.

The evidence for the separate existence of the dihydroxide (I) is as follows. A 4% solution of Lewisite-I oxide (possibly II) in benzene can be obtained by boiling the dry polymerised oxide (III) for a long time with this solvent. The solution is vesicant, and on storage deposits colourless crystals which soon change to the amorphous white polymer. When this benzene solution is shaken with water the arsenic content of the benzene drops *slowly* during some hours. Only a 1% solution of lewisite oxide in water can be obtained by leaving the constituents in contact. When this solution is shaken with benzene the arsenic content of the benzene slowly rises during some hours. The aqueous solution has a pH of 6·8, but by allowing Lewisite-I to remain in contact with water containing chalk a 2·8% solution can be obtained; and a solution of still higher normality can be obtained in aqueous sodium hydrogen carbonate of pH about 8. Thus the dihydroxide of Lewisite-I is, like that of phenyldichloroarsine, a very weak acid giving soluble salts.

Lewisite-I however is decomposed by *cold* caustic alkali as follows:

$$\mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2 + (OH)^- \longrightarrow Cl^- + C_2H_2 + As(OH)_3}$$

In the cold (16°), only alkaline solutions of pH 10·5 or more will bring about this decomposition, but at 50° solutions of pH 9 or more are effective. Prolonged boiling with water alone brings about some decomposition of Lewisite-I oxide.

It is significant that the curves shown in Figs. 1—4 show no irregularities indicative of the existence of hydroxy-chlorides R·AsCl·OH.

Alkyl-oxy- and -thio-derivatives of Lewisite-I and its Analogues.—The vesicant character of arsenicals such as Lewisite-I and phenyldichloroarsine is not a property of the $\mathrm{AsCl_2}$ group, since carefully prepared solutions of the corresponding oxides or dihydroxides are equally vesicant. In order to enhance the lipoid solubility of 2-chlorovinyldihydroxyarsine and its analogues, a number of derivatives of the general type $\mathrm{R{\cdot}As(OR')_2}$ has been made by the action of sodium alkoxides on the arsenical vesicants. The products are all volatile, vesicant, liquids which are hydrolysed *irreversibly* on contact with water.

A number of analogous thioethers $\mathrm{R{\cdot}As(SR')_2}$ has also been made. These are very slightly soluble in water and in general are hydrolysed *reversibly*, giving toxic, and sometimes vesicant, solutions, though the equilibrium $\mathrm{R{\cdot}As(SR')_2 + 2H_2O \rightleftharpoons R{\cdot}As(OH)_2 + 2R'SH}$ generally favours thioether formation (cf. Cohen, King, and Strangeways, *J.*, 1931, 3043; Barber, *J.*, 1932, 1365).

Aqueous and alcoholic solutions of sodium diethyldithiocarbamate, and its analogues, react readily with Lewisite-I to give crystalline solids of sharp melting-point which are very useful for the characterisation of the arsenical war gases. These dithiocarbamates are much more stable than are the simple thioethers of the alkyldichloroarsines, but only in cyclic structures, such as that given by " B.A.L." (Peters, Stocken, and Thompson, *Nature*, 1945, **156**, 616) does the degree of hydrolysis become negligible. Alkali hydrolyses all these compounds rapidly, acetylene being evolved from the Lewisite-I derivatives. Hydrogen peroxide also breaks up the ethers and thioethers in neutral or acid solution, giving free arsonic acids which are much less toxic than the corresponding tervalent substituted arsines.

Compound Formation with Dioxan.—When pure Lewisite-I is mixed with an equimolecular proportion of dioxan, heat is evolved and the whole mass solidifies on cooling to an addition product, m. p. 58—59°. This however dissociates into its constituents both when vaporised and when dissolved in anhydrous solvents such as benzene or chloroform. Di-2-chlorovinylchloroarsine (Lewisite-II) and tri-2-chlorovinylarsine (Lewisite-III) do not give similar products, and hence Lewisite-I may be separated in this way from these associated compounds. Arsenic trichloride also forms crystalline addition compounds with both dioxan and thioxan, but few of the other arsenical war gases, such as ethyldichloroarsine and phenyldichloroarsine, seem to react. The arsenic trichloride–dioxan adduct has been previously described by Doak (*J. Amer. Pharm. Soc.*, 1934, **23**, 541).

EXPERIMENTAL.

Quantitative Hydrolysis of Lewisite-I and Phenyldichloroarsine.—The results shown in Figs. 1—4 were obtained by dissolving a weighed amount of carefully fractionated Lewisite-I or phenyldichloroarsine in 50 ml. of benzene and shaking the solution with a known volume of water for ½ hour at 17°. Figs. 1 and 3 show the relation between the amount of the vesicant, $\mathrm{R{\cdot}AsCl_2}$, which remains as such in the benzene layer and the acidity attained by the aqueous layer.

The points indicated as " hydrolysis by hydrochloric acid " show that the degree of hydrolysis depends on the acidity of the aqueous phase and not on its total volume. Figs. 2 and 4, which refer to hydrolysis by water alone, show the extent to which the vesicants are hydrolysed on admixture with limited quantities of water. Again the degree of hydrolysis is independent of the initial concentration in the benzene layer.

			Found.					Required.				
Arsine, AsR_3.	B. p.	Formula.	C, %.	H, %.	As, %.	Cl, %.	Equiv.	C, %.	H, %.	As, %.	Cl, %.	Equiv.
Dimethoxy-2-chlorovinyl-	59°/6 mm.	$C_4H_8O_2ClAs$	—	—	—	17·8	98·6	—	—	—	17·9	99·2
Diethoxy-2-chlorovinyl-	71°/3 mm.	$C_6H_{12}O_2ClAs$	—	—	—	15·5	113	—	—	—	15·7	113
Diisopropoxy-2-chlorovinyl-	80°/3 mm., 88°/6 mm.	$C_8H_{16}O_2ClAs$	—	—	—	13·8	127	—	—	—	13·9	127
Diamyl-2-chlorovinyl-	130—138°/3 mm.	$C_{12}H_{24}O_2ClAs$	—	—	—	—	155	—	—	—	—	155
Diisooctyl-2-chlorovinyl-	184—186°/2 mm.	$C_{18}H_{36}O_2ClAs$	—	—	—	—	198	—	—	—	—	197
Diallyl-2-chlorovinyl-	99°/4 mm.	$C_8H_{12}O_2ClAs$	—	—	—	13·9	125	—	—	—	14·2	125
Di-(2-ethoxyethoxy)-2-chlorovinyl-	150°/3 mm.	$C_{10}H_{16}O_4ClAs$	—	—	—	11·4	155	—	—	—	11·3	157
Dimethoxyethyl-	129°/760 mm.	—	—	—	44·1	—	—	—	—	44·4	—	—
Methoxydiphenyl-	138°/2 mm., 150°/7 mm.	$C_{13}H_{13}OAs$	—	—	—	—	130	—	—	—	—	130
Methyldimethoxy-	111°/760 mm.	$C_3H_9O_2As$	—	—	—	—	76	—	—	—	—	76
Methyldiethoxy-	137°/760 mm.	$C_5H_{13}O_2As$	—	—	—	—	89	—	—	—	—	90
Methyldimethylthio-	75—77°/2 mm.	$C_3H_9S_2As$	—	—	40·4	—	—	—	—	40·7	—	—
Methyldiphenylthio-	195—198°/1 mm.	$C_{13}H_{13}S_2As$	—	—	24·5	—	—	—	—	24·5	—	—
Methyldi-p-*tolylthio-*	230°/0·5 mm.	$C_{15}H_{17}S_2As$			(S, 18·4)					(S, 19·0)		
Diphenylthio-2-chlorovinyl-	180—190°/2 mm. (decomp.)	—										
Di-(NN-*diethylthiocarbamylthio*)-2-*chlorovinyl-*[1]	m. p. 87°	$C_{12}H_{22}ClS_4N_2As$	32·6	5·1	17·4	—	—	33·3	5·1	17·3	—	—
Di(*morpholine-4-thiocarboxythio*)*methyl-* *[2]	m. p. 178°	$C_{11}H_{19}O_2S_4N_2As$	32·0	4·65	18·0	—	—	31·9	4·6	18·1	—	—
Di(*morpholine-4-thiocarboxythio*)*ethyl-* *[3]	m. p. 154°	$C_{12}H_{21}O_2S_4N_2As$	33·5	5·0	17·3	—	—	33·6	4·9	17·5	—	—
Di(*morpholine-4-thiocarboxythio*)-2-*chlorovinyl-* *[4]	m. p. 161°	$C_{12}H_{18}O_2ClS_4N_2As$	31·3	4·0	16·2	—	—	31·3	3·9	16·3	—	—
Di(*morpholine-4-thiocarboxythio*)*phenyl-* *[5]	m. p. 218—219°	$C_{16}H_{21}O_2S_4N_2As$	40·5	4·45	15·9	—	—	40·3	4·4	15·8	—	—

* $[O<([CH_2]_2)_2>N\cdot CS\cdot S]AsR$. [1] $(NEt_2\cdot CS\cdot S)_2As\cdot CH{:}CHCl$, crystd. from EtOH (Found: S, 29·4. Reqd.: S, 29·6%). [2] Needles from aqueous acetone. [3] Prisms from aqueous acetone. [4] Highly refracting rectangular plates. [5] Small needles or spherical aggregates.

Partition Coefficient of Lewisite-I Oxide.—The solution of the oxide in water was shaken with benzene, and samples of each layer, removed at intervals, were analysed for arsenic by addition of excess of iodine and back-titration with standard arsenite solution in the presence of sodium hydrogen carbonate. The following figures show that the equilibrium between the benzene-soluble oxide and the water-soluble dihydroxide is attained only slowly.

	Partition coefficient, $C_{H_2O}/C_{C_6H_6}$.			
Time of shaking (mins.)	10	60	120	1020
Initial aqueous solution + Benzene	8·13	4·74	2·63	1·67
Initial benzene solution + Water	0·07	0·23	0·26	0·69

The influence of the hydrogen carbonate buffer on the partition coefficient is shown by the following figures :

Lewisite + benzene + excess of aqueous $NaHCO_3$:	$C_{H_2O}/C_{C_6H_6}$ 13·5
Lewisite oxide (II or III) in benzene + aqueous $NaHCO_3$:	$C_{H_2O}/C_{C_6H_6}$ 13·4

Fission of Lewisite-I by the Hydroxyl Ion.—Lewisite-I hydroxide solution was prepared by adding 1 g. of Lewisite-I to 400 ml. of very dilute sodium hydrogen carbonate solution, shaking the mixture until reaction was complete, and acidifying cautiously with dilute hydrochloric acid until pH 7 was reached (B.D.H. Universal Indicator). 10-Ml. samples of this solution were added to 20 ml. of a buffer and maintained at 17°. Fission was detected by adding to each solution 1 ml. of ammoniacal cuprous chloride solution. A reddish-brown precipitate of cuprous acetylide indicated that fission had occurred. Results were :

Buffer used.	Reaction time (hours) before test.			
	2	6	17	24
4% Na_2HPO_4, pH 8·5	–	–	–	–
4% Borax, pH 9·5	–	–	Trace	Slight
4% K_2CO_3, pH 10·5	+	+	+	+

From similar experiments at 50° it was found that at this temperature fission was appreciable at pH 9·5 after 1 hour: 1% (or stronger) solutions of sodium carbonate gave evidence of fission at 50° after only 15 minutes.

A 4% solution can be obtained by boiling Lewisite-I oxide (III) with water for some time; if, however, the evolved vapours are led into ammoniacal cuprous chloride solution a positive acetylene reaction is obtained though a solution of Lewisite-I oxide prepared in the cold gives no positive reaction with this reagent.

Lewisite-I itself, when similarly boiled with water, gives no positive reaction for acetylene.

When administered (*a*) as droplets of Lewisite to the skin, (*b*) by injection, or (*c*) as dihydroxide by mouth, to experimental animals, Lewisite-I is slowly excreted in the form of its water-soluble dihydroxide and can be detected throughout the digestive system and particularly in the urine, by the cuprous chloride reaction which is sensitive to 0·001 mg. and can be used for approximate quantitative assay.

Derivatives of Lewisite-I and its Analogues.—The new compounds shown in the table were prepared in the course of this investigation. Values recorded as As,% were determined iodometrically after destruction of organic matter. The values recorded as equiv. were obtained by titrating the compound directly with iodine, to covert ter- into quinque-valent arsenic.

Adducts with Dioxan and Thioxan.—When equimolar amounts of Lewisite-I and dry dioxan were mixed, considerable heat was generated and, on cooling, the mixture solidified to a mass of white crystals. Recrystallised from light petroleum (b. p. 40—60°) the ***compound*** formed long colourless needles, m. p. 58—59° [Found : C, 24·3; H, 3·5%; equiv. (As), 146, 148; equiv. (Cl), 148·5. $C_6H_{10}O_2Cl_3As$ requires C, 24·37; H, 3·86%; equiv. (Cl or As), 147·5]. The " equiv. (As) " was determined as recorded above. The " equiv. (Cl) " was determined by titration in acid solution with silver nitrate, which reacts only with the chlorine bound to arsenic. The complex is almost completely dissociated in solution, as shown by molecular-weight determinations : Found : (cryoscopic in benzene) 145; (ebullioscopic in benzene) 195, 198; (ebullioscopic in chloroform) 124. Required : 124.

The arsenic trichloride dioxan complex, prepared in the same way, formed colourless crystals, m. p. 68—70°, from light petroleum, and had the composition assigned to it by Doak (*loc. cit.*) [Found: C, 23·0; H, 3·8%; equiv. (As), 158; equiv. (Cl), 105·0. Calc. for $3(C_4H_8O_2),2AsCl_3$: C, 22·9; H, 3·8%; equiv. (As), 156·6; equiv. (Cl), 104·4]. The molecular weight (cryoscopic in benzene) was 119; the required value is 627, so that the substance is strongly dissociated in solution, as stated by Doak.

The ***arsenic trichloride–thioxan*** complex, similarly prepared, formed colourless needles, m. p. 70—72° [Found: C, 16·8; H, 2·78%; equiv. (As), 143·5; equiv. (Cl), 96·0. $C_4H_8OSCl_3As$ requires C, 16·8; H, 2·8%; equiv. (As), 142·6; equiv. (Cl), 95·1]. Molecular-weight determination (cryoscopic in benzene) gave a value of 147 (Required : 285), again indicating almost complete dissociation.

The authors express their thanks to Mr. W. E. Hanby for assistance in the study of the hydrolysis of phenyldichloroarsine and to Mr. T. V. Healy for help in the preparation of a few of the dithiols. They thank the Chief Scientific Officer of the Ministry of Supply for permission to publish this paper, which describes work which was completed in 1939—40.

CHEMICAL DEFENCE EXPERIMENTAL STATION
(MINISTRY OF SUPPLY).

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6. *The Chemistry of Ribose and its Derivatives. Part II. The Constitution of an Anhydro-*D*-ribose.*

By G. R. Barker and M. V. Lock.

An anhydroribose prepared by the method of Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) has been examined and found to be bimolecular. Oxidation of the anhydride with sodium metaperiodate has been investigated and a crystalline *tetramethyl di-*D*-ribose anhydride* has been prepared and hydrolysed to 2 : 3-dimethyl D-ribose. Of three possible structures for the anhydride that corresponding to 1 : 5′-5 : 1′-diribofuranose anhydride is the most probable.

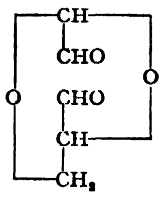
In an attempt to prepare 1 : 2 : 3-triacetyl D-ribofuranose by removal of the triphenylmethyl (trityl) grouping from 1 : 2 : 3-triacetyl 5-trityl D-ribofuranose, Bredereck, Köthnig, and Berger (*Ber.*, 1940, **73**, 956) obtained a compound which they claimed was 1 : 5-anhydro-D-ribofuranose. This structure was based on the failure of the compound to reduce Fehling's solution until after hydrolysis and a positive test for adjacent *cis*-hydroxyl groups with copper sulphate and alkali. However, it must be borne in mind that a number of different types of non-reducing anhydro-sugars are known, some monomeric and some dimeric, and that the structure postulated for the anhydroribose is by no means a unique interpretation of the experimental evidence. Our doubts as to the truth of the constitution assigned were aroused by the melting point of the compound (229—230°), which is unexpectedly high for a monomeric anhydride, compared with the melting point of D-ribose itself, variously given as 86—87° (Levene and Jacobs, *Ber.*, 1909, **42**, 1198) and 95° (van Ekenstein and Blanksma, *Chem. Weekblad*, 1913, **10**, 664). It was therefore decided to examine further the properties of the anhydride.

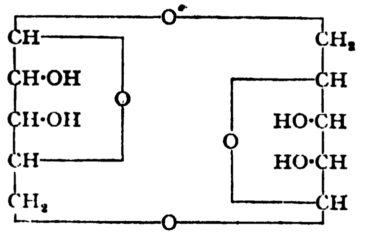
These studies have now reached a point at which it is clear that we have an anhydride not conforming in structure to that postulated by Bredereck and his co-workers. It will be seen from the results presented below that although it is probable we are dealing with the same compound we are unable to reproduce the specific rotation recorded previously. It is therefore considered desirable to place our observations on record in order that the question of the identity of the two materials may be considered by the German workers.

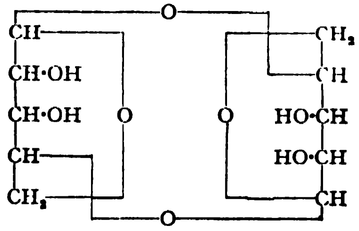
Trityl ribose and triacetyl trityl ribose were prepared and were found to correspond in properties with those previously recorded. By carrying out the acetylation without prior isolation of the trityl ribose the yield of the acetylated material was considerably improved. From triacetyl 5-trityl ribose prepared in either way were obtained an acetyl anhydroribose and an anhydroribose of which the melting points coincided with those recorded by Bredereck and his co-workers. The anhydroribose, however, had, in water, $[\alpha]_D^{19\cdot5}$ +11°, whereas this was previously recorded as +78°. All other properties of our materials were identical with those recorded by Bredereck.

Oxidation of the anhydride by sodium metaperiodate resulted in the consumption of 1 mol. of oxidant per mol. of ribose and no formic acid was liberated. If the constitution put forward by Bredereck and his co-workers for the anhydroribose is correct, then the product of the above oxidation would be 2 : 4-diformyldioxolan (I), produced in a similar manner from *lævo*glucosan, D-altrosan, or D-mannosan. This compound is known to have $[\alpha]_D^{20}$ −15° (Jackson and Hudson, *J. Amer. Chem. Soc.*, 1940, **62**, 958; Richtmyer and Hudson, *ibid.*, p. 961; Knauf, Hann, and Hudson, *ibid.*, 1941, **63**, 1447), whereas the solution obtained after oxidising our anhydroribose with sodium metaperiodate had an observed rotation which corresponded to $[\alpha]_D^{13}$ −48°, calculated on the assumption of the presence of the above dialdehyde. It appeared improbable, therefore, that our anhydride had the structure claimed by Bredereck for his material. Furthermore, cryoscopic determination of the molecular weight of the anhydroribose in aqueous solution indicated that the compound was dimeric. The possibility that the compound was exhibiting an anomalous depression of freezing point in aqueous solution was excluded by the fact that cryoscopic determination of the molecular weight of the acetylated anhydride in benzene confirmed the dimeric nature of the material (cf. Jackson *et al.*, *J. Res. Nat. Bur. Stand.*, 1929, **3**, 27; 1930, **5**, 733; 1931, **6**, 709). It is concluded that the anhydroribose consists of two molecules of ribose united with loss of two molecules of water in such a way that both reducing groups are involved in the union and two pairs of adjacent hydroxyl groups are present in the molecule.

Hydrolysis of the acetylated anhydride with boiling aqueous acid, followed by examination of the hydrolysate on the paper chromatogram using Partridge's method (*Nature*, 1946, **158**, 270), indicated that ribose was the only fission product. The rotation of the solution was also in agreement with this conclusion. It appears therefore, that no ether bridge is present, but that the ribose residues are joined by two glycosidic linkages. In order to establish which hydroxyl groups of the ribose radicals are thus combined in the anhydride, the tetra-acetyl diribose anhydride was methylated with methyl sulphate following Haworth and Streight's method (*Helv. Chim. Acta*, 1932, 15, 609, 693) and *tetramethyl di-*D*-ribose anhydride* was obtained which did not reduce Fehling's solution. This material was hydrolysed by boiling aqueous acid and the product, when examined on the paper chromatogram, moved as one component. In view of the observation of Hirst, Hough, and Jones (*J.*, 1949, 928) that certain isomeric methylated sugars can be separated by partition chromatography, it seemed likely from the above results that tetramethyl di-D-ribose anhydride is split by acid hydrolysis into two identical molecules. Evidence in agreement with this view was obtained by further studies of the methylated anhydride. No dimethyl ribose has yet been described and, since it seemed highly probable that hydrolysis of the methylated anhydride would produce a dimethylated ribose, recourse was made to methods involving oxidation with the periodate ion. Moreover, a method was required whereby the homogeneity of the product of acid hydrolysis, suggested by partition chromatography, could be confirmed. Oxidation of the acid hydrolysate with periodic acid produced no formic acid, but 0·45 mol. of formaldehyde was produced as shown by the method of Jeanloz (*Helv. Chim. Acta*, 1944, 27, 1509). Both results indicate that two molecules of 2 : 3-dimethyl ribose are produced from the methylated anhydride by acid hydrolysis. First, during the oxidation of methylated sugars with the periodate ion, formic acid is produced by oxidation of a reducing group adjacent to a free hydroxyl group or of a 1 : 2 : 3-trihydric alcohol system. It can be concluded, therefore, that in the acid hydrolysate from the tetramethyl di-D-ribose anhydride there can be no ribose derivative in which position 2 is unmethylated, no monomethyl ribose, and no free ribose, any of which would have yielded formic acid. Since there are the four original methoxyl groups of the methylated anhydride to be accounted for, and no ribose or monomethyl ribose is present, the methylated anhydride must be split into two molecules of dimethyl ribose, both of which are methylated at position 2. Furthermore, since the anhydroribose itself consumes two mols. of sodium metaperiodate it must contain two 1 : 2-glycol groupings and hence the tetramethyl derivative possesses two pairs of adjacent methoxyl groups. 2 : 3-Dimethyl D-ribose, therefore, is the sole product of hydrolysis of tetramethyl D-diribose anhydride. The production of formaldehyde during the oxidation by periodic acid is also in agreement with this conclusion. Formaldehyde is produced by periodate oxidation of a 1 : 2-glycol of which one hydroxyl group is primary and. of those sugars allowed by the other evidence discussed above, this condition is fulfilled only by 2 : 3-dimethyl ribose. If, however, 2 : 3-dimethyl ribose is the sole product of acid hydrolysis of tetramethyl di-D-ribose anhydride, the production of two mols. of formaldehyde would be expected during the oxidation of the hydrolysate of this compound with periodic acid. The low yield of formaldehyde obtained in these experiments is consistent with previous findings (Bell, *J.*, 1948, 992 : Jeanloz, *loc. cit.*) that some methylated sugars are incompletely oxidised by periodic acid and it has been stated


(I.)


(II.)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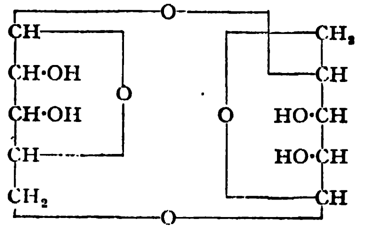
(IV.)

(Bell, *loc. cit.*) that, while the detection of formaldehyde is a useful qualitative test for the presence of a free primary hydroxyl group, it is not susceptible of quantitative use. The low yield of formaldehyde is not, therefore, considered to alter in any way the validity of the previous statement that 2 : 3-dimethylribose is the sole product of hydrolysis from tetramethyl di-D-ribose anhydride.

From the results of the experiments summarised above it follows that the anhydroribose possesses one of the structures (II), (III), and (IV). No convenient method of distinguishing between these structures is at present available but the formation of either (III) or (IV) from 1 : 2 : 3-triacetyl 5-trityl ribose would involve an interchange of furanose and pyranose forms, which although not impossible, is not suggested by any evidence so far obtained. We therefore consider that our anhydroribose is 1 : 5′-5 : 1′-diribofuranose anhydride (II). The configurations at the glycosidic centres of the two ribose residues are not known, but it seems possible that the discrepancy between the rotations of our material and that of Bredereck, Köthnig, and Berger is due to isomerism at these positions.

EXPERIMENTAL.

Acetyl groups were determined by Alicino's method (*Analyt. Chem.*, 1948, **20**, 590).

1 : 2 : 3-*Triacetyl* 5-*Trityl* D-*Ribofuranose*.—(*a*) 5-Trityl D-ribose was acetylated following the method of Bredereck *et al.* (*loc. cit.*) (Found : OAc, 25·0. Calc. for $C_{30}H_{30}O_8$: OAc, 24·9%).

(*b*) A solution of D-ribose (11·6 g.), dried in a vacuum over phosphoric oxide at 60°, and trityl chloride (21·6 g.) in pyridine (116 c.c.), distilled three times from phosphoric oxide, was maintained at 37° for 4 days, with the exclusion of moisture, and then, after being heated at 70° for 30 minutes, was cooled to 5°, and acetic anhydride (60 c.c.) and anhydrous pyridine (50 c.c.) were added. The solution was set aside for a further 24 hours and was then poured into ice-water (3 l.) containing one drop of saturated aqueous trisodium phosphate. This assisted the coagulation of the precipitate which, after 30 minutes, was collected by filtration and purified as described by Bredereck *et al.* (*loc. cit.*) (Found : C, 71·8; H, 5·8; OAc, 22·8. Calc. for $C_{30}H_{30}O_8$: C, 69·5; H, 5·8; OAc, 24·9%). The yield (30 g.) of this material was approx. three times that obtained by using the method of the German workers, and although it probably contained a small quantity of triphenylmethyl acetate it was quite satisfactory for subsequent experiments, contamination being removed as triphenylmethyl bromide.

*Tetra-acetyl Di-*D*-ribose Anhydride*.—1 : 2 : 3-Triacetyl 5-trityl D-ribofuranose, prepared by either method, yielded by use of the procedure of the German workers, tetra-acetyl di-D-ribose anhydride in the form of needles, m. p. 168·5—169·5° [Found : C, 50·0; H, 5·5; OAc, 39·6%; *M* (cryoscopic in benzene), 428. Calc. for $C_{18}H_{24}O_{12}$: C, 50·0; H, 5·6. OAc, 39·8%; *M*, 432·2]. This material (62·1 mg.) was heated at 97° with N/10-hydrochloric acid (3 c.c.) for 165 minutes by which time the solution had $[\alpha]_D^{18\cdot5}$ $-21\cdot6°$ (calculated on the assumption of the presence of D-ribose), unchanged on further heating. Under similar conditions D-ribose had $[\alpha]_D^{18\cdot5}$ $-21\cdot2°$. The solution obtained from the above hydrolysis was examined on the paper chromatogram alongside a specimen of authentic D-ribose, following Partridge's method (*loc. cit.*), an R_F value of 0·23 being obtained in each case. Partridge records a value of 0·21 for D-ribose.

*Di-*D*-ribose Anhydride*.—Tetra-acetyl di-D-ribose anhydride was deacetylated as described by Bredereck *et al.* (*loc. cit.*) and gave di-D-ribose anhydride in the form of colourless plates, m. p. 229° after sintering from 224° [Found : C, 45·7; H, 5·8%; *M* (cryoscopic in water), 246. Calc. for $C_{10}H_{16}O_8$: C, 45·5; H, 6·1%; *M*, 264). In water the material had $[\alpha]_D^{19\cdot5}$ $+11°$ (*c*, 0·68). After 24 hours at 28° the compound had consumed 1·01 mols. of sodium metaperiodate, no formic acid being detected by titration with N/100-sodium hydroxide after destruction of periodate ions. The solution obtained after completion of this oxidation had $[\alpha]_D^{18}$ $-48°$, calculated on the assumed presence of 2 : 4-diformyldioxolan.

*Tetramethyl Di-*D*-ribose Anhydride*.—Tetra-acetyl di-D-ribose anhydride (0·091 g.) in acetone (10 c.c.) was stirred at 55°, and methyl sulphate (3·2 c.c.) and aqueous sodium hydroxide (8·6 c.c.; 30%) were added portionwise every 15 minutes during 2·5 hours. Further portions of acetone (5 c.c.) were added to aid mixing. Water (4 c.c.) was added and, after the temperature had been allowed to rise to 75° for 5 minutes, the reaction mixture was cooled to room temperature and extracted 12 times with chloroform (20 c.c. each). The combined chloroform extracts were dried ($MgSO_4$) and after distillation of the solvent the residual syrupy *tetramethyl di-*D*-ribose anhydride* crystallised when kept at 0°. It separated from light petroleum (b. p. 80—100°) in needles and plates (0·045 g.), m. p. 129·5—130° after sintering at 125° (Found : C, 52·9; H, 7·5; OMe, 37·4. $C_{14}H_{24}O_8$ requires C, 52·5; H, 7·5; OMe, 38·7%). The compound did not reduce Fehling's solution.

*Examination of the Products of Hydrolysis of Tetramethyl Di-*D*-ribose Anhydride*.—Tetramethyl di-D-ribose anhydride (10 mg.) was heated at 97° with N/10-hydrochloric acid (2 c.c.) for 40 minutes. This treatment had been found in a preliminary experiment to bring about complete hydrolysis of the material as shown by measurements of reducing power using Somogyi's method (*J. Biol. Chem.*, 1926, **70**, 599). After removal of chloride ions by grinding with silver oxide and filtration, the solution was examined on the paper chromatogram by Partridge's method (*loc. cit.*). One component was observed having an R_F value of 0·55. A further sample of the tetramethyl compound (4·946 mg.) was hydrolysed as above, N-sodium hydrogen carbonate (10 c.c.) and potassium periodate (6 c.c. of a 2·3% solution in N/3-sulphuric acid at 45°) were added (the pH of the solution was then 7·5), and the solution was set aside at room temperature for 24 hours. After destruction of excess of periodate ions, formaldehyde was determined by Jeanloz's method (*loc. cit.*). The formaldehyde–dimedon complex (2·03 mg.) had m. p. 188—190° alone or mixed with an authentic specimen. A third sample of tetramethyl di-D-ribose anhydride (4·076 mg.) was hydrolysed as before, and, after being kept with sodium metaperiodate for

50 hours at room temperature, no liberation of formic acid could be detected using the method of Halsall Hirst, and Jones (*J.*, 1947, 1427).

One of us (M. V. L.) thanks the Department of Scientific and Industrial Research for the award of a maintenance grant.

THE UNIVERSITY, MANCHESTER, 13. [*Received, August 12th*, 1949.]

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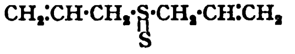
7. *The Structure of Diallyl Disulphide.*

By FREDERICK CHALLENGER and DOUGLAS GREENWOOD.

Diallyl disulphide reacts with triphenylphosphine yielding triphenylphosphine sulphide and diallyl monosulphide, with zinc yielding zinc sulphide and diallyl monosulphide, and with phenyl *iso*cyanide, followed by aniline, yielding *s*-diphenylthiourea. These reactions are explained by a free-radical mechanism involving the intermediate compounds $Ph_3P(S{\cdot}C_3H_5)_2$, $Zn(S{\cdot}C_3H_5)_2$, and $Ph{\cdot}N{:}C(S{\cdot}C_3H_5)_2$ which were, however, not isolated.

An alternative explanation, assuming a branched-chain structure $R_2S{:}S$ for diallyl disulphide, is disproved by a reaction with cysteine whereby cystine and prop-2-ene-1-thiol are obtained in good yield. Dimethyl, diethyl, and di-*p*-nitrophenyl disulphide also react in this way with cysteine. Dimethyl and diethyl disulphide do not react with zinc or triphenylphosphine.

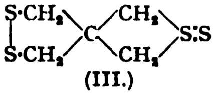
SEMMLER (*Arch. Pharm.*, 1892, **230**, 434) isolated diallyl disulphide from oil of garlic and found that on distillation with zinc dust it yielded diallyl monosulphide. He recorded no experimental details but we have confirmed his result. To explain this, it could be assumed that diallyl disulphide had a branched-chain structure (I) rather than the normal straight-chain structure (II).

(I.) 

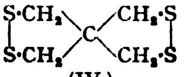
$$CH_2{:}CH{\cdot}CH_2{\cdot}\underset{\overset{\|}{S}}{S}{\cdot}CH_2{\cdot}CH{:}CH_2$$

$$CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}CH_2{\cdot}CH{:}CH_2 \quad \text{(II.)}$$

The preparation of disulphides of type (I) by Backer and Evenhuis (*Rec. Trav. chim.*, 1937, **56**, 129) lends some support to this view: tetrakisbromomethylmethane and sodium or



(III.)



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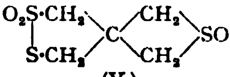

(V.)

potassium disulphide in alcohol give product (III) instead of the expected (IV); one atom of sulphur was removable by the action of sodium, copper, or sodium sulphide leaving the compound $C_5H_8S_3$, or by oxidation giving sulphuric acid and a disulphone (V) or the derived disulphonic acid $(HO_3S{\cdot}CH_2)_2C{<}{CH_2 \atop CH_2}{>}SO_2$ according to conditions.

Cavallito, Buck, and Suter (*J. Amer. Chem. Soc.*, 1944, **66**, 1952) regarded the naturally occurring antibacterial substance allicin as $CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}\underset{\overset{\downarrow}{O}}{S}{\cdot}CH_2{\cdot}CH{:}CH_2$ or $CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}O{\cdot}S{\cdot}CH_2{\cdot}CH{:}CH_2$. Small, Bailey, and Cavallito (*ibid.*, 1947, **69**, 1710) and Stoll and Seebeck (*Helv. Chim. Acta*, 1948, **31**, 189) concluded from a comparison of chemical and antibacterial properties that allicin was also obtained by the direct oxidation of diallyl disulphide with perbenzoic acid or hydrogen peroxide. This favours the structure (II) rather than the branched-chain (I).

It seemed possible that diallyl disulphide could have structure (II) and yet react with zinc as stated by Semmler, if dissociation into free radicals were assumed:

$$C_3H_5{\cdot}S{\cdot}S{\cdot}C_3H_5 \rightleftharpoons 2C_3H_5{\cdot}S{-} \xrightarrow{Zn} Zn(S{\cdot}C_3H_5)_2 \longrightarrow ZnS + (C_3H_5)_2S.$$

Such a reaction would be analogous with those observed by Schönberg, Rupp, and Gumlich (*Ber.*, 1933, **66**, 1932) with di(thio-α-naphthoyl) disulphide and metallic zinc or silver. We find that *bisallylthiozinc* cannot be isolated from the reaction between zinc and diallyl disulphide, but it has been prepared and found to decompose in the manner shown at temperatures (80—100°) much below those at which the reaction was carried out (120—130°).

It was therefore decided to investigate certain reactions of diallyl disulphide, which should enable a decision to be reached between structures (I) and (II).

We have recently (*Biochem. J.*, 1949, **44**, 87) shown that diallyl disulphide in cultures of the mould *Scopulariopsis brevicaulis* yields prop-2-ene-1-thiol and methyl allyl sulphide, thus behaving in the same way as saturated alkyl disulphides (Challenger *et al.*, *J.*, 1937, 868; 1938, 1872). This favours structure (II). On the alternative structure (I), the formation of hydrogen sulphide and allyl sulphide would be expected, but this was not observed. Moreover, diallyl monosulphide yields no prop-2-ene-1-thiol in cultures of *S. brevicaulis*, but volatilises apparently unchanged, as does also diethyl sulphide (Challenger and North, *J.*, 1934, 70; North, Thesis, Leeds, 1933). The formation of the thiol and methyl allyl sulphide from the disulphide in mould cultures cannot therefore be explained by the further breakdown of diallyl monosulphide formed as an intermediate compound from a disulphide of structure (I).

Schönberg (*Ber.*, 1945, **68**, 162) used triphenylphosphine for the detection of free radicals arising from disulphides by homolytic fission. Later, in a private communication (cf. this vol., pp. 892, 889), Schönberg classified disulphides into two groups, according to their reaction with triphenylphosphine: (1) unreactive, *e.g.*, diethyl and dibenzyl disulphide, and (2) those reacting to give Ph_3PS, probably by way of $Ph_3P(SR)_2$, *e.g.*, di-(*p*-dimethylaminophenyl) and dibenzoyl disulphide.

Some disulphides, *e.g.*, Ph_2S_2, oxidise triphenylphosphine to triphenylphosphine oxide in presence of water, probably by way of the intermediate compound $Ph_3P(SR)_2$ which was not isolated.

$$R_2S_2 \rightleftharpoons 2R{\cdot}S{\cdot} \xrightarrow{Ph_3P} Ph_3P(SR)_2 \xrightarrow{H_2O} Ph_3P{:}O + 2R{\cdot}SH$$

The disulphide was often regenerated from the resulting thiol by the oxygen of the air. The reactions of compounds of class 2 recall the formation of triphenylphosphine sulphide from triphenylphosphine and dithiocyanogen, doubtless through the unstable $Ph_3P(SCN)_2$ (Challenger, Smith, and Paton, *J.*, 1933, 1055).

We find that diallyl disulphide with triphenylphosphine at 80—90° with or without water gives triphenylphosphine sulphide in good yield, and therefore falls into group 2. Diallyl monosulphide was also formed and was characterised in one experiment as the *sulphilimine.*

Schönberg (*loc. cit.*) showed that certain disulphides of group 2 did not react with phenyl *iso*cyanide in conditions where elementary sulphur would form phenyl *iso*thiocyanate. He therefore concluded that Ph_3PS arose from $Ph_3P(SR)_2$ and not from free sulphur formed in solution by dissociation of a disulphide to a monosulphide and sulphur. However, with diallyl disulphide we obtained evidence of the formation of phenyl *iso*thiocyanate, *s*-diphenylthiourea being obtained after reaction with aniline. This appears to favour formula (I); yet the free radicals of diallyl disulphide might be more reactive than those of the disulphides tested by Schönberg, and might react to give $PhN{:}C(S{\cdot}C_3H_5)_2$ (VI). This could then (*a*) break down directly to allyl monosulphide and phenyl *iso*thiocyanate which, with aniline, would give the thiourea or (*b*) (VI) might itself react with aniline thus:

$$PhN{:}C(S{\cdot}C_3H_5)_2 + NH_2Ph \longrightarrow (Ph{\cdot}NH)_2C(S{\cdot}C_3H_5)_2 \longrightarrow (C_3H_5)_2S + CS(NHPh)_2.$$

Scheme (*a*) is perhaps more likely because of the ease with which most compounds of the type $X(S{\cdot}C_3H_5)_2$ (where X is, *e.g.*, a metal or Ph_3P) break down to XS and allyl sulphide. However, if either of the above schemes is correct, it renders this reaction useless for distinguishing between a free-radical mechanism and formation of elementary sulphur.

Triphenylstibine, although less reactive than triphenylphosphine, gives compounds which are more stable than those of triphenylphosphine (Challenger and Wilson, *J.*, 1927, 209). No reaction occurred between triphenylstibine and diallyl disulphide.

The symmetrical structure (II) for diallyl disulphide is supported by the work of Koch (*J.*, 1949, 394) on the ultra-violet absorption spectra of disulphides and has now been established by the reaction of diallyl disulphide with cysteine yielding cystine and prop-2-ene-1-thiol in over 90% yield. If diallyl disulphide had structure (I), it would be impossible to explain this reaction: production of hydrogen sulphide might be expected (no trace of this was detected), and any further reduction could not by any mechanism yield over 50% of the thiol. For structure (II), the reaction appears as a normal reductive fission of a disulphide, accompanied by oxidation of cysteine to cystine. Cysteine seems not to have been used as a reducing agent for simple disulphides, although Harrison (*Biochem. J.*, 1927, **21**, 1408) found that the oxidation of cysteine, by the oxygen of the air and by methylene blue, is catalysed by biscarboxymethyl disulphide; the activity disappeared if the disulphide link were destroyed, *e.g.*, by oxidation with bromine. Bersin and Steudel (*Ber.*, 1938, **71**, 1015) found that cysteine and biscarboxymethyl disulphide come to a 50% equilibrium with cystine and thioglycollic acid in aqueous solution. We found this type of reaction to occur also with dimethyl disulphide which gave methanethiol and cystine in 97% yield; diethyl and di-*n*-butyl disulphide required heat and gave lower yields, and a slow decomposition of the cysteine yielded hydrogen sulphide (for a similar decomposition of cysteine in aqueous solution see Mörner, *Z. physiol. Chem.*, 1904, **42**, 354, and Routh *J. Biol. Chem.*, 1939, **130**, 297). Di-*p*-nitrophenyl disulphide also yields the thiol and cystine.

Dimethyl and diethyl disulphide did not react with triphenylphosphine (cf. Schönberg, *loc. cit.*). They reacted hardly at all with zinc, even when heated, in contrast to statements that alkyl disulphides yield bisalkylthiozinc (Richter, "Organische Chemie," 11th edn., 1909, Vol. I, p. 162; Houben, "Die Methoden der Organischen Chemie," 1922, Vol. II, p. 365).

ADDENDUM.

It seemed possible that, in a high-boiling solvent and in absence of moisture (see p. 27), triphenylphosphine sulphide might also be formed from the phosphine and diphenyl disulphide. We failed to find any. In mesitylene or in nitrobenzene the phosphine oxide, but no sulphide, was isolated. We then found that in these solvents or in "liquid paraffin," but not in benzene, at the b. p. in presence of air the oxide is formed even in absence of diphenyl disulphide. From the phosphine and diphenyl disulphide in boiling mesitylene in absence of moisture and under nitrogen, neither the oxide nor the sulphide was obtained, although some triphenylphosphine oxide was formed when the reaction mixture was then left in contact with air at room temperature. In a private communication (27th May, 1949) Professor Schönberg states that he has observed independently that "triphenylphosphine reacts with the oxygen of the air at high temperatures, especially in the presence of light."

Schönberg *et al.* (*loc. cit.*) consider that several reactions of disulphides are best explained on the assumption of a homolytic dissociation into free radicals, *e.g.*, the action of metals and of triphenylmethyl giving RS·Metal and R·S·CPh$_3$, and the observation that certain disulphides do not obey Beer's dilution law. Waters (" Free Radicals," Oxford Univ. Press, 1946, pp. 72—73) accepts this free-radical mechanism.

The authors adopted this view in the present paper. A Referee has, however, suggested an alternative explanation of the reaction with triphenylphosphine. Polarisation of R_2S_2, thus $\overset{+}{\mathrm{RS}}\overset{\curvearrowright}{—}\overset{-}{\mathrm{SR}}$, might lead to fission, the positive moiety being captured by the unshared electrons of the phosphorus to give the salt-like product $[\mathrm{Ph_3\overset{+}{P}{\cdot}SR}]\overset{-}{\mathrm{S}}\mathrm{R}$. This could then break down to Ph_3PS and R_2S (allyl sulphide) and with water would yield Ph_3PO and RSH. This, it was remarked, would be in accord with the accepted mechanism for the hydrolysis of the *iso*cyanides by acids.

We accept this as an alternative representation of the reaction; the ionisation of a disulphide and the capture of a positive methyl group by the unshared electrons of an arsenic or selenium atom were, in fact, suggested by one of us in earlier discussions of the mechanism of biological methylation (Challenger, Taylor, and Taylor, *J.*, 1942, 49; Challenger, *Chem. and Ind.*, 1942, **61**, 414; *Chem. Reviews*, 1945, **36**, 342). Similar considerations apply to the reaction between phenyl *iso*cyanide and diallyl disulphide.

EXPERIMENTAL.

Diallyl Monosulphide and Scopulariopsis brevicaulis *in Bread Cultures.*—Four 1-l. flasks, each containing 150 g. of bread-crumbs and 25 c.c. of distilled water, were sterilised at 120°, inoculated with spores from a potato–agar subculture of *S. brevicaulis*, and incubated for 6 days at 32° and for 3 days at room temperature. Diallyl monosulphide (0·25 g.), emulsified with 25 c.c. of sterile water, was then added with a sterile pipette to each flask. The flasks were connected in series by means of sterile rubber bungs and glass tubing, and sterile air passed through them, for 18 days, into 2 tubes containing 4% aqueous mercuric cyanide and 5 tubes containing 3% aqueous mercuric chloride. No precipitate formed in either of the cyanide tubes, but a white precipitate was produced in all the chloride tubes during the first 18 days. The white precipitate (3·8 g.) did not melt below 260°, but darkened and sintered above 190°. It was insoluble in the common organic solvents, and gave mercuric oxide with cold sodium hydroxide solution, and the odour of allyl sulphide with 6N-hydrochloric acid. The precipitate was thus the mercurichloride of allyl sulphide which had volatilised unchanged from the cultures.

Diallyl Disulphide.—Our sample of this compound (*Biochem. J.*, 1949, **44**, 90) (Found: C, 49·8; H, 7·23; S, 43·1. Calc. for $C_6H_{10}S_2$: C, 49·3; H, 6·85; S, 43·8%) apparently contained a trace of the monosulphide. The absence of thiol was shown by shaking with 4% mercuric cyanide solution, no precipitate being formed.

Diallyl Disulphide and Zinc.—5·0 G. of diallyl disulphide and 2·5 g. (slight excess) of zinc dust were mixed, and left at room temperature for 3 days. There was no change in odour or appearance after this time, or after maintaining the mixture at 60° for 2 hours and then at 100° for 2 hours. After 10 hours at 120—130°, the odour of disulphide was almost completely replaced by that of allyl monosulphide. The oil was then decanted from the zinc dust, and fractionated at 16 mm., giving (i) an almost colourless oil, b. p. 35—45° (2 c.c.), having the odour of allyl monosulphide (b. p. 40°/16 mm.), and (ii) an orange-red oil, b. p. 60—85° (2·5 c.c.), probably mainly unchanged diallyl disulphide (b. p. 78—80°/16 mm.). The first fraction was redistilled at 16 mm., a fraction being collected between 36° and 40°. Two drops of this were shaken with saturated chloramine-T solution. The precipitate, when separated and recrystallised from ethyl acetate–ligroin (b. p. 40—60°), had m. p. and mixed m. p. with authentic diallyl sulphilimine, 71°.

The zinc dust was only slightly changed in appearance, being slightly darker and coarser than previously. Addition of hydrochloric acid gave hydrogen sulphide, but no odour of a thiol. The product therefore contained zinc sulphide.

Bisallylthiozinc.—A few drops of prop-2-ene-1 thiol, shaken with excess of zinc acetate solution, gave immediately *bisallylthiozinc* as a white precipitate. This was separated after 30 minutes. It sintered from 120° to 200°. It was insoluble in the common organic solvents and was therefore purified by washing it with large quantities of water, alcohol, and ether (Found : Zn, 30·4. $C_6H_{10}S_2Zn$ requires Zn, 30·9%).

When it was refluxed with benzene for 10 minutes, decomposition occurred. The residual pale yellow powder on treatment with dilute hydrochloric acid gave the odour of hydrogen sulphide with only a very slight odour of thiol; it was unmelted below 270°, but showed a colour change at 200—220° characteristic of zinc sulphide.

The same decomposition was observed with dry bisallylthiozinc at 100°. The odour of allyl sulphide was noticed after 15 minutes. The product was extracted with a little alcohol, and the solution added to a saturated solution of chloramine-T, giving a crystalline precipitate, m. p. 70°. The mixed m. p. with authentic allyl sulphilimine was 71°. The residue, insoluble in alcohol, gave no odour of a thiol with dilute hydrochloric acid.

Allyl Sulphilimine.—13·6 g. of chloramine-T in about 200 c.c. of water, and 6 g. of diallyl monosulphide were shaken for 20 minutes. The product, which formed within a few seconds, was separated, dried, and recrystallised by addition of light petroleum (b. p. 40—60°) drop by drop to a solution in chloroform. After 3 such recrystallisations, the *sulphilimine* had the constant m. p. 72° (Found : C, 54·8; H, 6·1; N, 5·1. $C_{13}H_{17}O_2NS_2$ requires C, 55·1; H, 6·0; N, 5·4). It is converted into an oil on storage at room temperature for 3—4 days, or rapidly at 100°. At 0° the sulphilimine is stable for 3—4 weeks. No loss in weight is involved. The nature of this change will form the subject of a further communication.

Reaction of Dimethyl and Diethyl Disulphide with Zinc.—Heating dimethyl disulphide (10 hours at 100—110°) or diethyl disulphide (9 hours at 130°) with zinc, yielded no monosulphide, almost all the disulphide being recovered unchanged. Traces of $Zn(SR)_2$ were detected in each reaction by the slight odour of a thiol produced on addition of hydrochloric acid.

Diallyl Disulphide and Triphenylphosphine.—The disulphide (0·3 g.), triphenylphosphine (0·5 g.), and benzene (4 c.c.) were refluxed for 6 hours in the absence of water. On cooling, triphenylphosphine sulphide (0·4 g.) separated (m. p. and mixed m. p. 161—162°). The benzene solution was distilled, with addition of fresh benzene to the residue, until the odour of allyl sulphide had passed entirely into the distillate. This was then shaken for 45 minutes with an aqueous solution of chloramine-T to form the sulphilimine. Evaporation of the benzene at room temperature left a white solid which, when recrystallised once from chloroform–ligroin, had m. p. and mixed m. p. with allyl sulphilimine, 71°. Repetition of this experiment in toluene at 90° in presence of water again gave triphenylphosphine sulphide, m. p. 162—163° (161—162° on admixture with an authentic specimen, m. p. 161—162°). The m. p. of triphenylphosphine oxide (151°) was depressed to 123°.

Diphenyl Disulphide and Triphenylphosphine.—Triphenylphosphine (1 g.) was heated in boiling nitrobenzene (7 c.c.) for 6 hours. Evaporation then left a tarry residue, which on extraction with ligroin (b. p. 80—100°) for 1 hour and recrystallisation from benzene–ligroin yielded triphenylphosphine oxide (0·3 g.), m. p. 153—154° (mixed m. p. 154°).

The phosphine (0·2 g.) was heated in boiling mesitylene (2 c.c.) for 5 hours with precautions to exclude moisture from the apparatus. Cooling and addition of ligroin (b. p. 40—60°) gave 0·08 g. of the phosphine oxide, m. p. and mixed m. p. 156°.

The phosphine (0·5 g.), diphenyl disulphide (0·42 g.), and mesitylene (5 c.c.) (all dried over P_2O_5; the mesitylene then redistilled) were refluxed for 6 hours in a dried apparatus in a stream of nitrogen previously passed through alkaline pyrogallol, sulphuric acid, and phosphoric oxide. On cooling and addition of ligroin to a portion, no crystals appeared, showing that no phosphine oxide or sulphide had been formed. However, after storage in air in a closed flask for 10 days, addition of ligroin gave 0·12 g. of the phosphine oxide, m. p. 154° (mixed m. p. 155°). Distillation of the solvents in a stream of nitrogen left a red liquid residue, which when kept overnight in air and then treated with ligroin gave a further 0·13 g. of the phosphine oxide. The residue after evaporation of the ligroin slowly deposited diphenyl disulphide, m. p. and mixed m. p. 60°.

Diallyl Disulphide and Phenyl iso*Cyanide* (Experimental conditions were obtained from a private communication from Professor A. Schönberg).—Diallyl disulphide (3 g.), phenyl *iso*cyanide (2 g.; b. p. 64°/20 mm.) and benzene (25 c.c.) were refluxed for 8 hours. Aniline (2 g.) was then added, and refluxing continued for a further 3 hours, a colour change from bluish-green to orange-red being then observed. Orange crystals separated overnight and were removed and washed with cold benzene and ether. After recrystallisation from alcohol, the product (0·65 g.) had m. p. 153° alone and mixed with authentic *s*-diphenylthiourea. The benzene mother-liquor was washed with concentrated hydrochloric acid (to remove aniline and phenyl *iso*cyanide) and with water, dried (Na_2SO_4), and evaporated at 40—50 mm., giving a further quantity of orange solid and unchanged diallyl disulphide.

Diallyl Disulphide and Triphenylstibine.—The disulphide (1·0 g.) and triphenylstibine (2·5 g.) in ligroin (b. p. 80—100°; 50 c.c.) were refluxed for 30 hours. There was no reaction.

When twice these quantities were used without a solvent during 3 hours at 100° and 8 hours at 140°, a viscous liquid slowly formed; no solid product was isolated.

Diallyl Disulphide and Cysteine.—Cysteine hydrochloride (1·0 g.) in water (*ca.* 15 c.c.) was neutralised with 10% sodium hydrogen carbonate solution (*ca.* 5 c.c.), and diallyl disulphide (0·167 g.) added. After

56 hours at room temperature in a stream of nitrogen the reaction was complete. The nitrogen, with the volatile products, passed through 2 tubes containing 4% aqueous mercuric cyanide to absorb thiols, and 3 tubes containing 3% aqueous mercuric chloride to absorb unchanged disulphide. Bisallylthiomercury (0·358 g.), m. p. and mixed m. p. 72°, was obtained from the first cyanide tube. This represents 0·152 g. (91%) of diallyl disulphide. The white precipitate (0·097 g.) in the mercuric chloride tubes had the properties expected of a mercurated fission product of diallyl disulphide. It gave an odour of a thiol with hydrochloric acid and a precipitate of mercuric oxide with sodium hydroxide solution, and was unmelted below 270° (*Biochem. J.*, 1949, **44**, 89). It represented about 0·016 g. (10%) of diallyl disulphide. Experimentally, 1 g. of diallyl disulphide gives about 6 g. of mercuric chloride derivative.

Cystine (0·25 g.) was removed from the reaction flask. Alone and in admixture with authentic cystine its m. p. (decomp.) was 256—258°. It was equivalent to 0·153 g. or 91·5% of the disulphide used.

Dimethyl Disulphide and Cysteine.—0·078 G. of dimethyl disulphide and excess of cysteine hydrochloride solution (1 g. in *ca.* 15 c.c.), neutralised as before, were left in a stream of nitrogen, as in the previous experiment.

Bismethylthiomercury (0·238 g., 97·5%) was obtained from the first cyanide tube. After one recrystallisation from ethyl acetate, it had m. p. and mixed m. p. 174°. A trace of precipitate in the chloride tubes probably accounted for the remaining 2·5% as unchanged disulphide. Cystine (0·196 g., equivalent to 98% of the disulphide) was recovered.

Diethyl Disulphide and Cysteine.—The reaction was slow. The disulphide (0·074 g.) and cysteine hydrochloride (0·5 g.), neutralised as before, were heated at 100° in nitrogen for 2½ hours. The precipitate in the first cyanide tube contained a trace of mercuric sulphide and was purified by decomposing it with 70% hydrochloric acid, and aspirating the gas again into mercuric cyanide solution, followed by recrystallisation from alcohol. The bisethylthiomercury (0·034 g., representing 17% of the disulphide used) melted at 75° (76° on admixture with an authentic specimen). The cystine formed had m. p. and mixed m. p. 258° (decomp.).

*Di-*n*-butyl Disulphide and Cysteine.*—The disulphide (0·05 g.), cysteine hydrochloride (1·0 g.), and 3·5% sodium hydrogen carbonate solution (*ca.* 15 c.c.) were heated for 11 hours at 100° in nitrogen. The greenish-black precipitate (0·266 g.) from the mercuric cyanide gave scarcely any thiol with hydrochloric acid, and was insoluble in hot alcohol. It was mainly mercuric sulphide and as the quantity was so large, decomposition of the cysteine was suspected. Cysteine hydrochloride and aqueous sodium hydrogen carbonate evolved hydrogen sulphide slowly at 100°, and mercuric sulphide was gradually precipitated in the mercuric cyanide.

*Di-*p*-nitrophenyl Disulphide and Cysteine.*—The disulphide (0·5 g.; m. p. 181—182°; Willgerodt, *Ber.*, 1885, **18**, 331, gives m. p. 180—181°; Fromm and Wittmann, *ibid.*, 1908, **41**, 2264, give m. p. 182°) and cysteine hydrochloride (0·5 g.), neutralised with sodium hydrogen carbonate, were refluxed in 50% aqueous alcohol for 2½ hours, cooled, and poured into excess of dilute hydrochloric acid, thus precipitating the *p*-nitrothiophenol and any unchanged disulphide. The precipitate sintered without complete fusion at 76°. It was dissolved in dilute sodium hydroxide, filtered from a small amount of disulphide, and reprecipitated by dilute hydrochloric acid. When quickly dried, it had m. p. 77° (the recorded m. p. of *p*-nitrothiophenol; Willgerodt, *loc. cit.*; Fromm and Wittmann, *loc. cit.*) but was rapidly re-oxidised to the disulphide.

The cystine was recovered by neutralising the acid solution with sodium hydrogen carbonate. It had m. p. 252° (decomp.) alone or mixed with an authentic cystine.

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8. *Derivatives of Oxazolid-2 : 4-dione. Part I. The Alkylation of 5 : 5-Dimethyloxazolid-2 : 4-dione.**

By J. S. H. Davies and W. H. Hook.

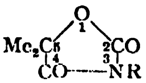
A number of *N*- and *O*-alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione has been prepared. The *O*-alkyl derivatives are shown to be 4-enol ethers and have been isomerised to the corresponding *N*-alkyl derivatives. The hydrolysis products of the *N*-alkyl derivatives have been studied.

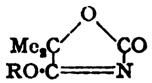
N-Alkyl derivatives of oxazolid-2 : 4-diones have been described by Ahlqvist (*J. pr. Chem.*, 1919, **99**, 77), who obtained 3-ethyloxazolid-2 : 4-dione by the hydrolytic desulphurisation of 2-thio-3 ethyloxazolid-4-one, and by Spielman (*J. Amer. Chem. Soc.*, 1944, **66**, 1244; cf. B.P. 561,183), who prepared 3-methyl derivatives of oxazolid-2 : 4-diones, having lower alkyl groups in the 5-position, by treating an aqueous alkaline solution of the appropriate oxazolid-dione with methyl sulphate. According to Spielman, methylation gave poor yields, and ethylation with

* Patents pending.

ethyl sulphate failed. The preparation of 5 : *5-dimethyl-3-ethyloxazolid-2 : 4-dione* (I; R = Et) by a modified procedure (anhydrous conditions) was reported in a preliminary communication (*Nature*, 1947, **160**, 610) and is more fully described below. It has since been possible to show that ethylation is effected to a limited extent by Spielman's aqueous alkylation procedure when reaction is prolonged (72 hours).

(I.)





(II.)

By treatment of the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione with ethyl iodide Spielman (*loc. cit.*) obtained a compound, m. p. 61—62°, which he considered to be 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. In contrast to the 3-methyl derivative, his product has now been shown to be unstable to dilute aqueous mineral acid which yields the original dione, and to aqueous alkali which yields the sodium salt of the dione. With ammonia in dry ethanol, it forms an *imino*-derivative, which is also hydrolysed by boiling hydrochloric acid to the original dione. This imino-derivative is not identical with *2-imino-5 : 5-dimethyloxazolid-4-one* prepared by condensation of ethyl α-hydroxy*iso*butyrate with guanidine (cf. Traube and Ascher, *Ber.*, 1913, **46**, 2077). Spielman's product is, therefore, now regarded as the 4-enol ethyl ether, *i.e.*, *4-ethoxy-5 : 5-dimethyloxazol-2-one* (II; R = Et). *4-Methoxy-* and *4-benzyloxy-5 : 5-dimethyloxazol-2-one* have also been prepared by Spielman's method. These enol ethers slowly isomerise when heated at 180°, alone or in the presence of the alkyl halide, to the *N*-alkyl derivatives identical with the products prepared as described below. If the alkyl group of the halide differs from that of the *O*-alkyl derivative, exchange occurs. Thus, the *O*-ethyl derivative is converted by methyl iodide at 180° into the *N*-methyl derivative, and benzyl bromide similarly furnishes the *N*-benzyl derivative.

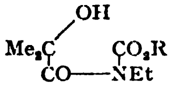
Although *O*-alkylation is the preponderating reaction between the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione and ethyl iodide at room temperature, an increasing amount of the *N*-ethyl derivative is formed as the temperature is raised. After 3 days in ether at room temperature, the product contains some 10% of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, whilst after 2 hours in boiling toluene 30% of this derivative is obtained. Work so far carried out suggests that the *O*-ethyl derivative is not necessarily an intermediate in the formation of the *N*-ethyl compound from the silver salt.

In view of the importance of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione (I; R = Me) in the treatment of "petit mal," myoclonic and akinetic epilepsies (Lennox, *J. Amer. Med. Assoc.*, 1945, **129**, 1069), improved methods for the alkylation of oxazolid-2 : 4-diones have been worked out, and new *N*-alkyl derivatives have been prepared for pharmacological investigation.

N-Alkylation of 5-substituted oxazolid-2 : 4-diones has now been found to proceed more readily and in good yield when the sodium or potassium salts are treated with an alkyl sulphate or halide under anhydrous conditions. Thus, when 5 : 5-dimethyloxazolid-2 : 4-dione in dry ethanol is treated first with sodium ethoxide and then with ethyl sulphate, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, m. p. 76—77°, is formed almost quantitatively, and this product is chemically similar to Spielman's 3-methyl derivative. Alternatively, alkylation may be carried out in excellent yield in acetone solution containing anhydrous potassium carbonate. Some *N*-alkyl derivatives are most conveniently prepared directly from ethyl α-hydroxy*iso*butyrate in one stage. The hydroxy-ester is condensed with urea in the presence of sodium ethoxide (Stoughton, *J. Amer. Chem. Soc.*, 1941, **63**, 2376) to form the sodium salt of 5 : 5-dimethyloxazolid-2 : 4-dione, and use of this solution directly for alkylation has furnished the 3-*n*- and -iso-*propyl*, 3-n- and -iso-*butyl*, 3-n- and -iso-*amyl*, *3-allyl*, *3-2′-methylallyl*, and *3-benzyl* derivatives.

The above methods have been extended to the introduction of substituted alkyl groups, the *3-2′-hydroxyethyl*, *3-2′-ethoxyethyl*, *3-2′-methylthioethyl*, and *3-acetoacetoxyethyl* derivatives having been thus prepared. 5 : 5-Dimethyl-3-2′-diethylaminoethyloxazolid-2 : 4-dione was very conveniently prepared from diethylaminoethyl chloride hydrochloride by the potassium carbonate–acetone method, the free base being liberated *in situ*.

N-Alkyloxazolid-2 : 4-diones are moderately stable to mineral acids, but are rapidly hydrolysed by aqueous sodium hydroxide, a reaction which is used as a method of assay (Spielman, *loc. cit.*). This hydrolysis, however, gives rise to two products—*sodium* N-*α-hydroxy*iso*butyryl*-N-*ethylcarbamate* (III; R = Na) and 1-(*ethylcarbamyl*)iso*propyl carbonate* (IV; R = Na). Acidification of the hydrolysis mixture causes decarboxylation of the latter to the hydroxyamide, whereas it is possible to isolate the free carbamic acid, which is fairly stable and may be determined in the solution by titration. Utilising these facts, it has been observed that the proportion of lactone hydrolysis, giving rise to (III), increases with the complexity of the *N*-alkyl substituent.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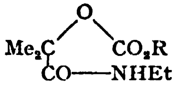
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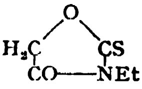
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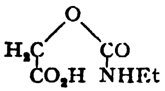
(VI.)

*α-Hydroxy*iso*butyroethylamide*, formed by decarboxylation of (IV; R = H) as above, is a low-melting solid, characterised as the 3 : *5-dinitrobenzoate*. It is also formed when (III; R = H) decomposes on being melted. This latter decarboxylation is accompanied by partial cyclodehydration, yielding the original 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. Decarboxylation occurs to the extent of 75% when (III; R = H) is heated alone or with copper powder, but when an aqueous solution of the acid is boiled with copper powder this amount is increased to 88%; in all cases the remaining acid undergoes cyclisation. On storage in aqueous solution at room temperature, the acid slowly cyclises and 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione crystallises from the solution.

By alkaline hydrolysis of 2-thio-3-ethyloxazolid-4-one (V) and treatment of the product with bromine, Ahlqvist (*loc. cit.*) obtained a product, which he considered to be *N*-ethylcarbamylglycollic acid (carboxymethyl *N*-ethylcarbamate) (VI). Hydrolysis and desulphurisation, by the method of Ahlqvist, of 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one, the preparation of which is described in Part III (*J.*, 1950, 36) also gives (III; R = H). It seems probable, therefore, that Ahlqvist's product is *N*-ethyl-*N*-glycollylcarbamic acid and not (VI).

In a publication which has appeared since the completion of this work, Spielman (*J. Amer. Chem. Soc.*, 1948, **60**, 1021) mentions the use of methanol as a solvent for the methylation procedure, the alkaline reagent presumably being sodium hydroxide as in his earlier experiments. He mentions also an alternative alkylation procedure, in which the potassium salt of the oxazoliddione is first formed by treating the dione in "Cellosolve" with potassium hydroxide. In the present work, alkylation proceeded most efficiently under strictly anhydrous conditions, and alkali-metal hydroxides were better replaced by alkoxides in alcoholic solution or anhydrous potassium carbonate in non-hydroxylic solvents.

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

O-Alkylation. 4-Ethoxy-5 : 5-dimethyloxazol-2-one.—In accordance with Spielman's procedure, a mixture of the dry silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione (60 g.), dry ether (400 c.c.), and ethyl iodide (50 g.) was set aside, with occasional shaking, at room temperature for 3 days. Filtration of the product and evaporation of the ether yielded a residue (22·4 g.), which was distilled. The fraction (10·4 g.), b. p. 90—91°/0·5 mm., partly solidified and was crystallised from dry ether, yielding a product (4·5 g.), m. p. 58—60°; recrystallisation raised the m. p. to 61—62°, which is that of the product described by Spielman and now considered to be 4-ethoxy-5 : 5-dimethyloxazol-2-one.

The total ether-soluble product (4·8 g.), obtained from 10 g. of silver salt as above was warmed with dilute hydrochloric acid for 15 minutes to convert the ethoxy-compound into 5 : 5-dimethyloxazolid-2 : 4-dione. The cooled mixture was made alkaline with sodium hydrogen carbonate to convert the latter into its sodium salt, and then extracted with ether. The ethereal extract yielded a crude residue (0·45 g.), which on crystallisation from ether afforded 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, identical with the product described below. Similarly, reaction of the silver salt (10 g.) with ethyl iodide in boiling toluene for 2 hours yielded a mixed product (4·5 g.), which after treatment with hydrochloric acid and sodium hydrogen carbonate afforded the crude 3-ethyl derivative (1·5 g.).

Reactions of 4-Ethoxy-5 : 5-dimethyloxazol-2-one (II; R = Et).—(*a*) Treatment with a slight excess of 2N-sodium hydroxide and back-titration with hydrochloric acid (phenolphthalein) gave equiv. = 155·7 (Calc., 157). Acidification of the liquors and ether-extraction yielded 5 : 5-dimethyloxazolid-2 : 4-dione. (*b*) Heating the ether alone in a sealed tube at 180° for 24 hours afforded, almost quantitatively, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. With ethyl iodide, conversion was almost complete after 18 hours at 180°, but only partial after 72 hours at 140°. (*c*) Heating the ether with methyl iodide at 180° for 18 hours yielded 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, and with benzyl bromide under similar conditions the 3-benzyl derivative (see below) was formed. (*d*) The *O*-ethyl compound (2·4 g.) in dry ethanol (20 c.c.) was treated with a stream of dry ammonia for 15 minutes. The ethanol was distilled off and the residue (2·2 g.) recrystallised from ethanol, *4-imino-5 : 5-dimethyloxazolid-2-one* being obtained as fine colourless prisms, m. p. 270—271° (decomp.) (Found: C, 46·8; H, 6·5. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·3%). When the imino-derivative was heated on a steam-bath for ½ hour with hydrochloric acid, ether-extraction of the resulting solution yielded 5 : 5-dimethyloxazolid-2 : 4-dione, m. p. 76—77°.

2-Imino-5 : 5-dimethyloxazolid-4-one was prepared by condensation of ethyl α-hydroxy*iso*butyrate with guanidine (cf. Traube and Ascher, *loc. cit.*). It crystallised from ethanol as colourless prisms, m. p. 245—246° (Found: C, 47·0; H, 6·4%). The mixed m. p. with the 4-imino-derivative was 200—210° (decomp.). The 2-imino-derivative was hydrolysed to 5 : 5-dimethyloxazolid-2 : 4-dione by heating it with hydrochloric acid.

4-Methoxy-5 : 5-dimethyloxazol-2-one.—The dry silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione in ethereal suspension was allowed to react with methyl iodide at room temperature for 3 days. Filtration and concentration of the ethereal solution yielded the 4-*methoxy*-derivative as fine colourless needles, m. p. 153—154°, sparingly soluble in ether (Found : C, 50·15; H, 6·2. $C_6H_9O_3N$ requires C, 50·35; H, 6·3%). It was isomerised to the 3-methyl derivative by heating it at 180° for 18 hours, and with alcoholic ammonia yielded 4-imino-5 : 5-dimethyloxazolid-2-one.

4-Benzyloxy-5 : 5-dimethyloxazol-2-one.—This *ether*, prepared similarly, by use of benzyl bromide, formed colourless needles, m. p. 147—148° (Found : N, 6·7. $C_{12}H_{13}O_3N$ requires N, 6·4%). When heated at 180° for 60 hours, it furnished the 3-benzyl analogue.

N-*Alkylation.*—The preparation of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione by method (*a*) below is typical of the *N*-alkylation procedure employed. For the introduction of higher alkyl groups the iodides were used, and for secondary halides or 2-substituted halides the time of reaction was longer. For *products* prepared see the table.

5 : 5-Dimethyl-3-ethyloxazolid-2 : 4-dione. (*a*) To a solution of sodium (4·6 g.) in dry ethanol (100 c.c.) were added dry urea (12 g.) and ethyl α-hydroxy*iso*butyrate (26·4 g.), prepared by the method of U.S.P. 2,349,795. The reaction mixture was refluxed for 16 hours, and dissolved ammonia then removed by drawing a current of dry air through the boiling solution. The mixture was treated dropwise, with stirring, with ethyl sulphate (30·8 g.) and then refluxed for 2 hours, and the ethanol removed by distillation. The residue was treated with iced water and extracted with ether, the extract dried, and the solvent was removed. 5 : 5-Dimethyl-3-ethyloxazolid-2 : 4-dione (21·5 g., 68·5%) crystallised from aqueous methanol as flat, vitreous prisms, m. p. 76—77° (Found : C, 53·7; H, 7·1. $C_7H_{11}O_3N$ requires C, 53·5; H, 7·1%).

(*b*) 5 : 5-Dimethyloxazolid-2 : 4-dione (25·8 g.) in dry acetone (200 c.c.) was stirred for 3 hours with anhydrous potassium carbonate (30 g.). Ethyl sulphate (30·8 g.) was added to the mixture, which was refluxed for 6 hours. After filtration from inorganic material, the product (27·5 g., 87%) was isolated by removal of solvent and working up as above.

(*c*) 5 : 5-Dimethyloxazolid-2 : 4-dione (12·9 g.) in a solution of sodium hydroxide (5 g.) in water (50 c.c.) was stirred vigorously at room temperature with ethyl sulphate (15·4 g.) for 72 hours. The crystalline solid which separated was crystallised from aqueous methanol, affording 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (3·1 g.) in 20% yield.

Hydrolysis of 5 : 5-Dimethyl-3-alkyloxazolid-2 : 4-diones.—(a) 3-*Ethyl derivative.* Aqueous sodium hydroxide (50 c.c.; 0·189 N.) was added to 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (1·011 g.) in alcohol (20 c.c.), and after 15 minutes the mixture was back-titrated with hydrochloric acid (12·0 c.c.; 0·249N.) using phenolphthalein (Found: equiv., 156·5. Calc. : equiv., 157). Hydrochloric acid (9·9 c.c.; 0·249N.) was then added to the neutral liquors until carbon dioxide was no longer liberated, the carbon dioxide was removed by suction, and the excess of hydrochloric acid determined by back-titration with sodium hydroxide (2·3 c.c.; 0·189N.). The amount of carbon dioxide liberated by decarboxylation was thus equivalent to 10·7 c.c. of the standard sodium hydroxide, indicating that about 31% of the oxazolid-2 : 4-dione had been hydrolysed to the carbonate, the remaining 69% having given the carbamate. When 2N-sodium hydroxide was used, the former figure was 32·6%.

3-*Alkyl derivatives of* 5 : 5-*dimethyloxazolid*-2 : 4-*dione.*

Derivative.	M. p.	B. p. at (mm.).	n_D^{20}.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
Pr^n	46—47°	—	—	$C_8H_{13}O_3N$	56·0	7·5	56·1	7·7
Pr^i	89 -90	—	—	$C_8H_{13}O_3N$	56·1	7·6	,,	,,
Bu^n	—	68—70° (0·6)	1·4455	$C_9H_{15}O_3N$	58·2	8·2	58·4	8·1
Bu^i	--	64—66 (0·7)	1·4446	$C_9H_{15}O_3N$	58·2	8·0	,,	,,
n-Amyl	---	80—81 (0·5)	1·4470	$C_{10}H_{17}O_3N$	60·6	8·3	60·3	8·6
*iso*Amyl	—	76—77 (0·7)	1·4456	$C_{10}H_{17}O_3N$	60·9	8·6	,,	,,
$CH_2{:}CH{\cdot}CH_2$	—	82 (4)	1·4590	$C_8H_{11}O_3N$	56·7	6·8	56·8	6·5
$CH_2{:}CMe{\cdot}CH_2$	—	85—87·5 (1·8)	1·4611	$C_9H_{13}O_3N$	58·8	7·6	58·9	7·1
$C_6H_5{\cdot}CH_2$	60—61	—	—	$C_{12}H_{13}O_3N$	65·9	6·1	65·8	6·0
$HO{\cdot}CH_2{\cdot}CH_2$	—	119 (0·7)	1·4695	$C_7H_{11}O_4N$	48·6	6·6	48·6	6·4
$EtO{\cdot}CH_2{\cdot}CH_2$	—	76 (0·3)	1·4460	$C_9H_{15}O_4N$	54·0	7·8	53·7	7·5
$MeS{\cdot}CH_2{\cdot}CH_2$	39—40	110 (1·0)	—	$C_8H_{13}O_3NS$	47·2	6·5	47·3	6·4
$Et_2N{\cdot}CH_2{\cdot}CH_2$ *	23—24	107 (2·0)	—	$C_{11}H_{20}O_3N_2$	58·5	8·85	57·8	8·8
,, hydrochloride	190	—	—	$C_{11}H_{21}O_3N_2Cl$	50·0	8·1	49·9	8·0
,, methiodide	129—130	—	—	$C_{12}H_{23}O_3N_2I$	38·8	6·3	38·9	6·3
$Et_2N{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2$ †	34	141 (1)	—	$C_{12}H_{22}O_4N_2$	55·3	8·8	55·8	8·6
Hydrochloride	145	—	—	$C_{12}H_{23}O_4N_2Cl$	48·9	7·6	48·9	7·9
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2$ ‡	—	155 (0·7)	1·4713	$C_{11}H_{15}O_6N$	52·0	5·7	51·4	5·9

* Cf. Spielman (*loc. cit.*, 1948).

† 3-Diethylamino-2-hydroxypropyl chloride was prepared by the method of Price, Leonard, Peel, and Reitsema (*J. Amer. Chem. Soc.*, 1946, 68, 1807).

‡ 2-Chloroethyl acetoacetate was prepared as described by Jones, Robinson, and Strachan (*J.*, 1946, 87).

The neutral liquors from 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (10 g.) treated as above with sodium hydroxide (2N.) and hydrochloric acid (2N.), after liberation of carbon dioxide, were extracted continuously with ether and yielded *α-hydroxy*iso*butyroethylamide* as a hygroscopic soapy solid, m. p. 25—28°, which could not be purified further owing to a tendency to lose ethylamine when heated. It gave a 3 : *5-dinitrobenzoate*, m. p. 154° (Found : C, 48·4; H, 4·9. $C_{13}H_{15}O_7N_3$ requires C, 48·0; H, 4·6%). The aqueous mother-liquors from extraction of the amide, after acidification with hydrochloric acid and ether-extraction, yielded N-*α-hydroxy*iso*butyryl*-N-*ethylcarbamic acid* as colourless prisms (from ether), m. p. 122—123° (decomp.) (Found : C, 48·1; H, 7·4. $C_7H_{13}O_4N$ requires C, 48·0; 7·4%). The carbamic acid (0·535 g.) was heated at 130—140° for 15 minutes; the volume of carbon dioxide evolved was 51 c.c. (75%). When the product was heated on the steam-bath in an open flask with a cold finger inserted at the mouth, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione condensed on the cold finger. The residue, on reacting with 3 : 5-dinitrobenzoyl chloride, furnished the 3 : 5-dinitrobenzoate of α-hydroxy*iso*butyroethylamide.

(b) 3-*Methyl derivative.* Hydrolysis of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione was examined as for the 3-ethyl derivative, and the results indicated that about 40% of the hydrolysis occurred by fission of the N–C bond to yield the carbonate. α-Hydroxy*iso*butyromethylamide was readily obtained with m. p. 78—79° (cf. Spielman, *loc. cit.*) and afforded a 3 : *5-dinitrobenzoate*, m. p. 162° (Found : C, 46·5; H, 4·3. $C_{12}H_{13}O_7N_3$ requires C, 46·3; H, 4·2%). *N*-α-Hydroxy*iso*butyryl-*N*-methylcarbamic acid melted at 115° (decomp.).

(c) 3-iso*Propyl derivative.* Hydrolysis of 5 : 5-dimethyl-3-*iso*propyloxazolid-2 : 4-dione proceeded with the liberation of only 0·15 equivalent of carbon dioxide, indicating that hydrolysis of the lactone preponderated to the extent of 85%. N-*α-Hydroxy*iso*butyryl*-N-iso*propylcarbamic acid* had m. p. 150—151° (decomp.) (Found : C, 51·1; H, 8·1. $C_8H_{15}O_4N$ requires C, 50·8; H, 8·0%).

Hydrolysis of 2-Thio-5 : 5-dimethyl-3-ethyloxazolid-4-one (see Part III).—Aqueous sodium hydroxide (50 c.c.; 0·2N.) was added to 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one (1 g.) in alcohol (20 c.c.). After 15 minutes, bromine vapour was drawn through the mixture until it was no longer decolorised. The solution was then made acid to Congo-red with dilute hydrochloric acid, and extracted with ether. Partial evaporation of the extract yielded *N*-α-hydroxy*iso*butyryl-*N*-ethylcarbamic acid, m. p. 122—123°, identical with the compound described above.

British Schering Research Institute,
Alderley Edge, Cheshire.

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9. *Derivatives of Oxazolid-2 : 4-dione. Part II. O- and N-Alkylation of 5-Substituted Oxazolid-2 : 4-diones.**

By J. S. H. Davies, M. E. H. Fitzgerald, and W. H. Hook.

A number of new *N*-alkyl derivatives of 5-substituted oxazolid-2 : 4-diones has been prepared. In the reaction of the silver salts of oxazolid-2 : 4-dione and its 5-substituted derivatives with alkyl halides, 5-substitution favours *O*-alkylation.

Spielman (*J. Amer. Chem. Soc.*, 1944, **66**, 1244; 1948, **70**, 1021) has reported the preparation of a number of *N*-alkyl derivatives of oxazolid-2 : 4-diones. The formation of *O*-alkyl derivatives of 5 : 5-dimethyloxazolid-2 : 4-dione and an improved method for the *N*-alkylation of 5 : 5-dimethyloxazolid-2 : 4-dione have been reported in Part I (preceding paper). This work has now been extended in part to oxazolid-2 : 4-dione and to the 5-methyl, 5-methyl-5-ethyl, 5-benzyl-5-methyl, 5-phenyl-5-methyl, and 5 : 5-diphenyl derivatives. The *N*-alkyl derivatives described herein and in Part I have been tested for anti-convulsant activity in mice; detailed results will be published elsewhere.

The oxazolid-2 : 4-diones were prepared from the corresponding glycollic esters by the method of Stoughton (*J. Amer. Chem. Soc.*, 1941, **63**, 2376; U.S.PP. 2,349,313, 2,349,785, 2,372,861). The glycollic esters were prepared by known methods, but in some cases esterification was more efficient by the azeotropic procedure described by Clarke and Davis (*Org. Synth.*, Coll. Vol. I, p. 261) for ethyl oxalate. *Ethyl α-hydroxy-β-phenyl*iso*butyrate*, which was prepared by a modification of Stoughton's method, has not previously been described.

N-Alkylation of 5-substituted oxazolid-2 : 4-diones by the action of the alkylating agent on an alcoholic solution of the sodium salt of the dione, as reported earlier, proceeded normally, but with oxazolid-2 : 4-dione, itself, the yields were in some cases low, probably owing to the high solubility of the products in water.

It was shown (Part I) that reaction of the silver salt of 5 : 5-dimethyloxazolid-2 : 4-dione with ethyl iodide in ether at room temperature caused mainly *O*-ethylation with about 10% of *N*-ethylation, but that in boiling toluene up to 30% of the *N*-ethyl derivative was obtained. The silver salt of oxazolid-2 : 4-dione itself, with methyl iodide, gave only the *N*-methyl derivative, 3-methyloxazolid-2 : 4-dione, although the presence of a small proportion of

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* Patents pending.

O-methylation product was indicated by the formation of a trace of high-melting product, believed to be 4-imino-oxazol-2-one, when the reaction product was treated with ammonia.

In contrast, the silver salt of 5-benzyl-5-methyloxazolid-2 : 4-dione with ethyl iodide in ether at room temperature readily afforded *4-ethoxy-5-benzyl-5-methyloxazol-2-one*, and the silver salt of 5 : 5-diphenyloxazolid-2 : 4-dione with ethyl iodide in boiling benzene readily gave *4-ethoxy-5 : 5-diphenyloxazol-2-one*; a search for 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione revealed only traces. The amount of *O*- relative to *N*-alkylation in this reaction thus varies with substitution in the 5-position in the order diphenyl- > dimethyl- > unsubstituted oxazolid-2 : 4-dione.

The above-mentioned oxazolones have been isomerised to the corresponding 3-ethyloxazolid-2 : 4-diones by treatment at 180° with ethyl iodide as described in Part I.

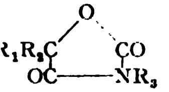
EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s and b. p.s are uncorrected.)

*Ethyl α-Hydroxy-β-phenyl*iso*butyrate*.—A mixture of benzyl methyl ketone (300 g.) and piperidine (2·5 c.c.) was added slowly during 15 minutes to anhydrous hydrogen cyanide (150 g.), with stirring and cooling. The temperature was allowed to rise to a maximum of 30° and, after completion of addition of the ketone, was reduced to 0°, and stirring was continued for 1 hour. The mixture was then added dropwise to fuming hydrochloric acid (600 c.c.) at 0°, saturated with gaseous hydrogen chloride, stirred at 0° for 4 hours, and allowed to attain room temperature overnight. It was then filtered from precipitated solid and neutralised with aqueous sodium hydroxide (40%), the temperature being maintained below 15°. The precipitate was filtered off and dried. Crystallisation from benzene furnished *α-hydroxy-β-phenyl*iso*butyramide* (211 g.), m. p. 83° (Found: C, 67·2; H, 7·0. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The acid was obtained by boiling the amide with sodium hydroxide solution (40%) for 1½ hours and was esterified by the azeotropic method of Clarke and Davis (*loc. cit.*). *Ethyl α-hydroxy-β-phenyl*iso*butyrate* was obtained as a colourless mobile oil, b. p. 141—142°/19 mm., in 65% yield (Found: C, 69·3; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

3-*Alkyloxazolid-2 : 4-diones*.—The products recorded in the table were prepared as described in Part I by condensing the appropriate α-hydroxy-esters with urea in presence of sodium ethoxide and alkylating the sodium salt of the dione so obtained. They crystallised from methanol, ethanol, or ether.

Preparation of 3-alkyloxazolid-2 : 4-diones,



							Found, %.		Required, %.		Yield,
R_1.	R_2.	R_3.	M. p.	B. p.	n_D^{20}.	Formula.	C.	H.	C.	H.	%.
H	H	Bu^n	·	137—139°/ 16 mm.	1·4614	$C_7H_{11}O_3N$	53·9	7·3	53·5	7·1	66
H	H	*n*-Amyl	—	144—148/ 15 mm.	1·4605	$C_8H_{13}O_3N$	56·8	8·0	56·2	7·7	51
H	H	$CH_2{\cdot}CH{:}CH_2$	—	72/5 mm.	1·4815	$C_6H_7O_3N$	51·2	5·3	51·1	5·0	23
H	H	$CH_2{\cdot}CMe{:}CH_2$	44—45°	143/13 mm.	—	$C_7H_9O_3N$	54·4	5·9	54·2	5·85	67
H	H	$CH_2{\cdot}C_6H_5$	44—45	—	—	$C_{10}H_9O_3N$	62·9	4·8	62·8	4·8	41
H	Me	$[CH_2]_2{\cdot}CH_3$	—	73—75/ 1 mm.	1·4531	$C_7H_{11}O_3N$	53·2	6·8	53·5	7·1	43
H	Me	$[CH_2]_3{\cdot}CH_3$	—	84—87/ 1 mm.	1·4530	$C_8H_{13}O_3N$	55·8	7·3	56·1	7·7	54
H	Me	$[CH_2]_4{\cdot}CH_3$	—	100/ 1·8 mm.	1·4545	$C_9H_{15}O_3N$	58·7	8·1	58·4	8·2	40
H	Me	$CH_2{\cdot}CMe{:}CH_2$	—	128/ 11 mm.	1·4709	$C_8H_{11}O_3N$	57·1	6·7	56·8	6·6	62
H*	Me	$CH_2{\cdot}COMe$	51—52	139—141/ 2·5 mm.	—	$C_7H_9O_4N$	49·2	5·3	49·1	5·3	70
Me	Et	Et	—	77/2·5 mm.	1·4447	$C_8H_{13}O_3N$	56·1	7·7	56·1	7·7	60
Me	Et	Bu^n	—	90—91/ 3 mm.	1·4459	$C_9H_{15}O_3N$	58·4	8·3	58·4	8·2	59
Me	Et	$CH_2{\cdot}CH{:}CH_2$	—	87·5/ 1·9 mm.	1·4593	$C_9H_{13}O_3N$	58·6	7·1	58·9	7·1	62
Me	CH_2Ph	Et	71—72	—	—	$C_{13}H_{15}O_3N$	67·4	6·7	67·0	6·4	70
Me	Ph	Me	—	168—169/ 18 mm.	—	$C_{11}H_{11}O_3N$	64·0	5·5	64·4	5·4	73
Ph	Ph	Et	90	—	—	$C_{17}H_{15}O_3N$	72·8	5·1	72·6	5·3	55

* *Semicarbazone*, m. p. 193—194°, from ethanol (Found: C, 42·6; H, 5·4. $C_8H_{12}O_5N_4$ requires C, 42·1; H, 5·3%).

Reaction of the Silver Salt of Oxazolid-2 : 4-dione with Methyl Iodide.—The dry silver salt of oxazolid-2 : 4-dione (10 g.), suspended in a mixture of dry ether and methyl iodide (20 c.c.), was set aside at room temperature for 3 days. Filtration, evaporation, and crystallisation of the residue from ether yielded 3-methyloxazolid-2 : 4-dione (0·75 g.), m. p. and mixed m. p. with an authentic specimen, 134°. Extraction of the filter cake with dry ethanol yielded a further quantity of the 3-methyl derivative. Treatment of the mother-liquors from these extractions with aqueous ammonia, and partial evaporation of the solvents, yielded a product (0·05 g.), presumably *4-imino-oxazol-2-one*, m. p. 215—220° (Found: C, 36·7; H, 3·9. $C_3H_4O_2N_2$ requires C, 36·0; H, 4·0%).

4-Ethoxy-5-benzyl-5-methyloxazol-2-one.—The dry silver salt of 5-benzyl-5-methyloxazolid-2 : 4-dione (11 g.) was suspended in a mixture of dry ether (100 c.c.) and ethyl iodide (20 c.c.), the mixture set aside for 3 days and the solid filtered off. The ether, on distillation, gave a residue (6·0 g.), which on crystallisation from ethanol yielded the *oxazolone* as colourless needles, m. p. 110—111° (Found: C, 67·3; H, 6·6. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·4%).

The oxazolone (1·0 g.) in ethyl iodide (5 c.c.) was heated in a sealed tube at 180° for 20 hours. The product was dissolved in ether, the ethereal solution washed with thiosulphate solution and with sodium carbonate solution, and the solvent distilled. The residue after crystallisation from ether gave 5-benzyl-5-methyl-3-ethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 71—72°.

4-Ethoxy-5 : 5-diphenyloxazol-2-one.—The dry silver salt (18 g.) of 5 : 5-diphenyloxazolid-2 : 4-dione was suspended in a mixture of dry benzene (150 c.c.) and ethyl iodide (15 c.c.). The mixture was boiled under reflux for 2 hours and then filtered and the solvent distilled off from the filtrate. The residue after 3 crystallisations from ether yielded *4-ethoxy-5 : 5-diphenyloxazol-2-one* as colourless prisms, m. p. 100—101° (Found: C, 72·5; H, 5·5. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3%). The total ethereal mother-liquors were shaken for ½ hour with warm dilute hydrochloric acid and then extracted with aqueous sodium hydrogen carbonate to remove 5 : 5-diphenyloxazolid-2 : 4-dione arising from the hydrolysis of any residual oxazolone. The ethereal solution was dried and the solvent distilled, leaving a residue (0·1 g.) from which by crystallisation from ether 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione, identical with an authentic specimen, was obtained.

The oxazolone (0·5 g.) in ethyl iodide (2 c.c.) was heated in a sealed tube at 180° for 20 hours. The product was dissolved in ether, the solution washed with aqueous sodium thiosulphate, and the solvent distilled off. Crystallisation of the residue from ether yielded 5 : 5-diphenyl-3-ethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 89—90°.

Our thanks are due to Mr. T. Deegan for some of the preparations, and to Miss Audrey Hudson for pharmacological tests.

British Schering Research Institute,
Alderley Edge, Cheshire.

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10. *Derivatives of Oxazolid-2 : 4-dione. Part III. The Alkylation of 2-Thio-oxazolid-4-ones.**

By J. S. H. Davies, W. H. Hook, and F. Long.

Alkylation of 2-thio-oxazolid-4-ones yields a mixture of the corresponding 2-thio-3-alkyl-oxazolid-4-ones and 2-alkylthio-oxazol-4-ones. The factors which influence the proportions of *N*- and *S*-alkylation are indicated. A number of 3-alkyloxazolid-2 : 4-diones has been prepared from the 2-thio-3-alkyloxazolid-4-ones.

In Parts I and II (preceding papers) the alkylation of the sodium and silver salts of oxazolid-2 : 4-diones has been examined and the results show that the sodium salts are alkylated in the 3-position, *i.e.*, on the *N*-atom, whilst the silver salts give a mixture of the 3-alkyl derivatives and 4-alkoxyoxazol-2-ones, the proportions depending on the temperature (lower temperatures favouring the formation of the latter) and the nature of the substituents in the 5-position. It was also shown that the 4-alkoxyoxazol-2-ones were isomerised by heat to the corresponding 3-alkyloxazolid-2 : 4-diones.

It became of interest, therefore, to examine the alkylation of 2-thio-oxazolid-4-ones, where the effect of tautomerism involving the 2- and 3-positions would be expected to be more pronounced than that of the 3- and 4-positions in oxazolid-2 : 4-diones. A second reason was the fact that 2-thio-3-alkyloxazolid-4-ones, like 2-thio-oxazolid-4-ones themselves, are readily converted into the corresponding oxazolid-2 : 4-diones by a variety of reagents, and the method affords another route to 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, which has been shown to be of value in the treatment of "petit mal" (Lennox, *J. Amer. Med. Assoc.*, **1945**, **129**, 1069).

Urech (*Ber.*, 1873, **6**, 1113; 1878, **11**, 467) has shown that 2-thio-5 : 5-dimethyloxazolid-4-one (I; R = H) is formed when an aqueous solution of potassium thiocyanate, potassium cyanide, and acetone is treated with hydrochloric acid. Erlenmeyer, Kleiber, and Loebenstein (*Helv. Chim. Acta*, 1938, **21**, 1010) have similarly prepared 2-thio-5-methyl-5-ethyloxazolid-4-one from methyl ethyl ketone and converted it into 5-methyl-5-ethyloxazolid-2 : 4-dione.

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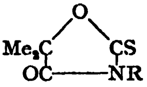
* Patents pending.

Improved conditions for the preparation of these two thio-oxazolidones by Urech's method have been developed and the method has been extended to the preparation of 2-thio-oxazolid-4-one from formaldehyde, and of *2-thio-5-methyloxazolid-4-one* from acetaldehyde. The method was most successful for the 5 : 5-dimethyl derivative, which is now readily obtained in 65—75% yield, although the reaction even in this case is very slow. The condensation with methyl ethyl ketone proceeds still more slowly, even on warming, partly owing to the lower solubility of the intermediate cyanohydrin, and the yield of product is much less; and attempts to condense benzyl methyl ketone and acetophenone with cyanide and thiocyanate under these conditions failed.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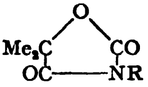
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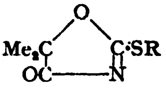
(III.)

The alkylation of 2-thio-5 : 5-dimethyloxazolid-4-one has been examined in alcohol, in other organic solvents, such as acetone and benzene, and in water in the presence and absence of various alkaline reagents. The best conditions for 3-alkylation have been applied to the preparation of various 2-thio-3-alkyloxazolid-4-ones and these compounds have been converted into the corresponding oxazolid-2 : 4-diones.

Ethylation of 2-thio-5 : 5-dimethyloxazolid-4-one with ethyl sulphate in ethanol in presence of one equivalent of sodium ethoxide gave an *N*-ethylation product, *2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one* (I; R = Et), and an *S*-ethylation product, *2-ethylthio-5 : 5-dimethyloxazol-4-one* (III; R = Et), which were separated by fractional distillation and crystallisation. The *N*-ethyl derivative is moderately stable to dilute mineral acid, but is hydrolysed by cold aqueous sodium hydroxide to *sodium* N-*α-hydroxy*iso*butyryl*-N-*ethylthiocarbamate* (cf. Part I). It can be determined by titration, as in the case of the 3-alkyloxazolid-2 : 4-diones (Spielman, *J. Amer. Chem. Soc.*, 1944, **66**, 1244), but the end-point is transient owing to the rapid cyclisation of the free thiocarbamic acid to re-form the thio-oxazolidone. 2-Ethylthio-5 : 5-dimethyloxazol-4-one is unstable in moist air and is rapidly hydrolysed by dilute mineral acids to 5 : 5-dimethyloxazolid-2 : 4-dione with evolution of ethanethiol; with aqueous alkali, the hydrolysis proceeds more slowly to form the alkali-metal salt of the oxazolid-dione, but with ammonia 2-imino-5 : 5-dimethyloxazolid-4-one is formed, which is identical with the product prepared by the method of Traube and Ascher (*Ber.*, 1913, **46**, 2077). Preliminary attempts to isomerise the *S*-ethyl to the *N*-ethyl compound were unsuccessful. Methylation of 2-thio-5 : 5-dimethyloxazolid-4-one also gave a mixture; the *S*-methyl derivative was not isolated, but its presence was shown by the evolution of methanethiol on acidification with dilute mineral acid and by the isolation of 5 : 5-dimethyloxazolid-2 : 4-dione from the hydrolysed product.

The ease of hydrolysis of the *S*-methyl derivative afforded a convenient method for the quantitative isolation of the *N*-methyl derivative. The total methylation product was treated with dilute hydrochloric acid, and the oxazolid-dione was separated from the *N*-methyl derivative by extraction with aqueous sodium hydrogen carbonate. This method has been applied throughout for determining the relative amounts of *S*- and *N*-alkylation products formed, the amount of *S*-alkylation being based on the weight of the recovered oxazolid-2 : 4-dione. In ethanol with methyl sulphate and sodium ethoxide, the yield of the 3-methyl derivative was 21% and with potassium ethoxide 27%, but in the absence of an alkaline reagent only *S*-methylation occurred.

In other non-aqueous solvents, such as acetone and benzene, 2-thio-5 : 5-dimethyloxazolid-4-one was methylated with methyl sulphate in presence of sodium, potassium, and barium carbonates, the yields in acetone being 31%, 44%, and 49%, respectively, and 20% with potassium carbonate in benzene; with no alkaline reagent present, only partial *S*-methylation took place. It is of interest that when ethylation is carried out in hot commercial dioxan with potassium carbonate and excess of ethyl sulphate the main reaction product is 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione. Presumably, the *S*-methyl derivative initially formed is decomposed by potassium carbonate in boiling dioxan, and the resulting oxazolid-dione is then re-alkylated. *2-Thio-3 : 5-dimethyloxazolid-4-one*, *2-thio-3 : 5-dimethyl-5-ethyloxazolid-4-one* and *2-thio-5-methyl-3 : 5-diethyloxazolid-4-one* were prepared by the acetone–potassium carbonate procedure. Benzylation of 2-thio-5 : 5-dimethyloxazolid-4-one in acetone with benzyl bromide and potassium carbonate for 1½ hours gave a small yield of the

S-benzyl derivative, which was isolated only with difficulty owing to the presence of considerable quantities of toluene-ω-thiol and higher-boiling, related products. The indications were, however, that *S*-benzylation largely predominated. With benzyl chloride for 14 hours, a low yield of 5 : 5-dimethyl-3-benzyloxazolid-2 : 4-dione was obtained.

When methylating 2-thio-5 : 5-dimethyloxazolid-4-one in aqueous solution, it was again found that the proportion of *N*-methylation varied with the nature of the alkaline reagent; with one molecular proportion of potassium hydroxide, the yield of the *N*-methyl derivative was 18% and of *S*-methyl derivative 64% (estimated as the oxazolid-2 : 4-dione); with three molecular proportions of potassium carbonate, the yield of the *N*-methyl derivative rose to 31% with a corresponding decrease in *S*-methylation, but with sodium carbonate or potassium hydrogen carbonate, the yield of the *N*-methyl compound was only about 20%. It will be seen from the foregoing and from the experimental section that the course of methylation is influenced by a number of factors. In aqueous solution, increased alkalinity of the reagent, *e.g.*, the use of potassium carbonate in place of hydrogen carbonate, and increase in size of the cation, *e.g.*, the use of potassium carbonate instead of sodium carbonate, favour *N*-methylation. In alcohol or acetone, the effect of the basic cation is still apparent, the highest yield (49%) of *N*-methylation product being obtained by methylating the barium salt of 2-thion-5 : 5-dimethyloxazolid-4-one in acetone. When considering the effect of solvent alone, it will be seen that the proportion of *N*-methylation increased in the order : benzene < water < alcohol < acetone.

The 2-thio-3-alkyloxazolid-4-ones were readily converted into the corresponding oxazoliddiones by treatment with chlorine or bromine water and also by acid permanganate.

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s and b. p.s are uncorrected.)

2-Thio-oxazolid-4-one.—Sodium cyanide (270 g., 5·5 mols.) and potassium thiocyanate (485 g., 5 mols.) were dissolved in water (550 c.c.) and formaldehyde solution (400 c.c., 5 mols.; 37%) was added with cooling and stirring. Concentrated hydrochloric acid (1,250 c.c.) was then added dropwise and the temperature kept below 10°. After filtration from the inorganic salts, the filtrate was set aside for 4 weeks and then continuously extracted with ether. The crude residue (211 g.), obtained after distilling off the ether, was crystallised from water and gave pure 2-thio-oxazolid-4-one (184 g.; 32%), m. p. 115—116° (Found: C, 30·85; H, 2·45; N, 12·4; S, 27·6. Calc. for $C_3H_3O_2NS$: C, 30·8; H, 2·6; N, 11·95; S, 27·4%). Ahlqvist (*J. pr. Chem.*, 1919, [ii], **99**, 56) gives m. p. 111—112°. The yield was raised to 40% by addition of concentrated sulphuric acid to the main filtrate (10% of the volume) and storage for 9 weeks.

By passing bromine vapour into its solution in aqueous methanol, the thio-oxazolidone gave oxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 89—91°.

2-Thio-5-methyloxazolid-4-one.—Sodium cyanide (54 g., 1·1 mols.) and potassium thiocyanate (97 g., 1 mol.) were dissolved in water (125 c.c.), and acetaldehyde (54 g., 1·2 mols.) was added slowly with stirring and good cooling, as much heat is evolved. Concentrated hydrochloric acid (250 c.c.) was added to the stirred mixture, the temperature being kept below 10°. The homogeneous solution was stirred for a further hour, and the inorganic salts were filtered off and washed with diluted hydrochloric acid (20 c.c.; 1 : 1 by vol.). After 1 week, the light-brown crystalline solid (32 g.; 25%) was collected, and sulphuric acid (40 c.c.) added to the filtrate, which on storage for a further 5 weeks deposited a second crop of crystals (38 g.; 29%). The united crops were crystallised from benzene, whereupon *2-thio-5-methyloxazolid-4-one* was obtained as rosettes of colourless, prismatic needles, m. p. 93—94° (Found: C, 37·0; H, 3·8. $C_4H_5O_2NS$ requires C, 36·65; H, 3·8%). The yield on a 5-molar scale was 47%.

2-Thio-5 : 5-dimethyloxazolid-4-one.—Sodium cyanide (270 g., 5·5 mols.) and potassium thiocyanate (65 g.) were dissolved in water (750 c.c.), and acetone (500 c.c., *ca.* 7 mols.) was added. The mixture was stirred and cooled to 0°, and concentrated hydrochloric acid (1,250 c.c.) slowly added during about 5 hours, the temperature being kept below 10°. After 1 hour's stirring the inorganic salts were filtered off and washed with dilute hydrochloric acid (125 c.c.; 1 : 1 by vol.). Potassium thiocyanate (420 g., total of 5 mols.) in water (400 c.c.) was then added to the filtrate kept below 5°. The inorganic salts which separated were filtered off and washed with diluted hydrochloric acid, and the filtrate and washings set aside for 7 days. The first crop of material (204 g.) was filtered off and concentrated sulphuric acid (200 c.c.) added to the filtrate. After 6 weeks another crop (323 g.) separated and after 12 weeks a third crop (19 g.). The united crops were dissolved in ether, the solution filtered from insoluble impurity, the solvent removed, and the residual 2-thio-5 : 5-dimethyloxazolid-4-one (531 g., 73%) crystallised in portions from water. The yield from acetone cyanohydrin and potassium thiocyanate after about 8 weeks was 64%.

2-Thio-5-methyl-5-ethyloxazolid-4-one.—The general procedure of the previous experiments was followed with methyl ethyl ketone (265 c.c., 3 mols.), sodium cyanide (135 g., 2·75 mols.), potassium thiocyanate (242·5 g., 2·5 mols.), water (315 c.c.), and concentrated hydrochloric acid (625 c.c.). Stirring was continued for 16 hours before filtering off the inorganic salts, which were washed with a mixture of water (25 c.c.) and concentrated hydrochloric acid (25 c.c.). The united filtrates and washings were stirred at 40—45° for 8 days and then set aside for 2 days. The yellow solid (155 g.) was filtered off, washed with diluted hydrochloric acid and dried at 50°. Concentrated sulphuric acid (100 c.c.) was added to the united filtrates and washings, followed by enough water to dissolve the oil on the surface of the solution; after 6 weeks a further crop (28 g.) was obtained. The united crops were dissolved in ether, the solution was filtered, and the solvent distilled from the clear filtrate. The residue, a light-yellow solid (140 g.; 35%), on crystallisation from hot water, furnished 2-thio-5-methyl-5-ethyloxazolid-4-one, colourless needles, m. p. 106°, as described by Erlenmeyer, Kleiber, and Loebenstein (*loc. cit.*).

2-*Thio*-3 : 5-*dimethyloxazolid*-4-*one*.—2-Thio-5-methyloxazolid-4-one (65·5 g., 0·5 mol.), acetone (300 c.c.), and potassium carbonate (87 g., 0·63 mol.) were stirred for 2 hours, methyl sulphate (72 g., 0·57 mol.) was added, and the mixture boiled under reflux for 3 hours; after removal of the acetone, water (200 c.c.) and concentrated hydrochloric acid (75 c.c.) were added in turn. Extraction with carbon tetrachloride, washing the extract with aqueous ammonia (2N.) and distillation of the dried solution gave a colourless oil, b. p. 134—146°/15 mm., which solidified, and crystallisation from a mixture of ether and light petroleum (b. p. 30—40°; 1 : 1 by vol.) gave 2-*thio*-3 : 5-*dimethyloxazolid*-4-*one* as prismatic needles (27·5 g.; 38%), m. p. 74—75° (Found: C, 41·9; H, 4·85. $C_5H_7O_2NS$ requires C, 41·4; H, 4·85%). A current of chlorine was passed through a mixture of the thion compound (20 g.) in carbon tetrachloride (30 c.c.) and water (30 c.c.). Ether-extraction and distillation furnished 3 : 5-dimethyloxazolid-2 : 4-dione as an oil (12·65 g.; 71%), b. p. 116—125°/22 mm. (Found: C, 46·95; H, 5·9. Calc. for $C_5H_7O_3N$: C, 46·5; H, 5·45%).

2-*Thio*-3 : 5-*dimethyl*-5-*ethyloxazolid*-4-*one*.—2-Thio-5-methyl-5-ethyloxazolid-4-one (31·8 g., 0·2 mol.) in acetone (120 c.c.) was stirred with anhydrous potassium carbonate (34 g., 0·25 mol.) for 2 hours until neutral. Methyl sulphate (28 g., 0·22 mol.) was added dropwise during ½ hour; heat was evolved and the mixture was boiled under reflux for 1½ hours. After removal of the solvent, the residue was stirred with water (80 c.c.), concentrated hydrochloric acid (75 c.c.) was then added and the methanethiol evolved burned in a current of coal gas. Extraction of organic material with carbon tetrachloride, removal of 5-methyl-5-ethyloxazolid-2 : 4-dione with dilute ammonia (100 c.c.; 2N.), drying (Na_2SO_4), and fractional distillation furnished 2-*thio*-3 : 5-*dimethyl*-5-*ethyloxazolid*-4-*one* (15·95 g.; 46%) as a colourless oil, b. p. 116—122°/14 mm., which solidified when kept and then melted at 30—33°. Crystallisation from light petroleum (b. p. 40—60°) yielded colourless, prismatic needles, m. p. 34° (Found: C, 48·75; H, 6·3; N, 8·6. $C_7H_{11}O_2NS$ requires C, 48·55; H, 6·35; N, 8·1%). A current of chlorine was passed into a solution of the thion compound (13·15 g.) in carbon tetrachloride (15 c.c.) and water (15 c.c.) for 1½ hours, the temperature being kept below 5°. After neutralisation and extraction with ether, removal of solvents gave an oil (9·9 g.), which on fractionation furnished 3 : 5-dimethyl-5-ethyloxazolid-2 : 4-dione (8 g.; 67%) as a colourless oil, b. p. 100—105°/16 mm. (Found: C, 53·7; H, 7·35; N, 8·25. Calc. for $C_7H_{11}O_3N$: C, 53·5; H, 7·05; N, 8·9%).

2-*Thio*-5-*methyl*-3 : 5-*diethyloxazolid*-4-*one*.—On replacement of the methyl sulphate by ethyl sulphate (32·4 g., 0·21 mol.) in the above experiment, addition of more acetone (total 250 c.c.), and boiling under reflux for 5 hours, 2-*thio*-5-*methyl*-3 : 5-*diethyloxazolid*-4-*one* was obtained first as an oil, b. p. 129—132°/35 mm., which solidified when kept and melted at 29—32°. Crystallisation from light petroleum (b. p. 40—60°) yielded large, colourless prisms (15·4 g.; 41%), m. p. 32—33° (Found: C, 51·4; H, 6·75; N, 8·1. $C_8H_{13}O_2NS$ requires C, 51·35; H, 6·95; N, 7·5%). On hydrolytic de-sulphurisation, the thion compound (12·7 g.) gave 5-methyl-3 : 5-diethyloxazolid-2 : 4-dione as a slightly yellow oil (8·85 g.), b. p. 100—102°/15 mm. (Found: N, 7·9. Calc. for $C_8H_{13}O_3N$: N, 8·2%).

2-*Thio*-5 : 5-*dimethyl*-3-*ethyloxazolid*-4-*one* and 2-*Ethylthio*-5 : 5-*dimethyloxazol*-4-*one*.—(*a*) 2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) was dissolved in a solution of sodium ethoxide obtained from sodium (4·6 g., 0·2 mol.) and dry ethanol (100 c.c.), and ethyl sulphate (30·8 g., 0·2 mol.) was added to the clear solution. After 6 hours' boiling under reflux, the solution was fractionally distilled in a vacuum. The fraction, b. p. 80—85°/1·5 mm., was crystallised from methanol, giving 2-*thio*-5 : 5-*dimethyl*-3-*ethyloxazolid*-4-*one* as colourless, glistening plates, m. p. 62—63° (Found: C, 48·9; H, 6·7; S, 18·9. $C_7H_{11}O_2NS$ requires C, 48·6; H, 6·4; S, 18·5%). The fraction, b. p. 85—90°/1·5 mm., crystallised from dry ether to give 2-*ethylthio*-5 : 5-*dimethyloxazol*-4-*one* as colourless, vitreous prisms, m. p. 27—28° (Found: C, 48·8; H, 6·6; S, 18·5%). When shaken with dilute hydrochloric acid, the oxazolone decomposed evolving ethanethiol and ether-extraction of the liquors gave 5 : 5-dimethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 76—77°. When shaken with aqueous amonia (2N.), the oxazolone deposited 2-imino-5 : 5-dimethyloxazolid-4-one, m. p. and mixed m. p. with an authentic specimen, 245—246°. The thio-oxazolidone (17·3 g., 0·1 mol.) in carbon tetrachloride (15 c.c.) was stirred with water (15 c.c.), and chlorine passed through for ¾ hour at below 10°. Excess of chlorine was removed by a current of air, the two layers were separated, and the aqueous layer was further extracted with carbon tetrachloride. The united extracts were then washed in turn with aqueous potassium hydrogen carbonate and sodium thiosulphate and then dried, and the solvent distilled off. The residue, on crystallisation from ether, afforded 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione, in 90% yield, having m. p. and mixed m. p. with an authentic specimen, 76—77°.

(*b*) 2-Thio-5 : 5-dimethyloxazolid-4-one (145 g., 1 mol.) was dissolved in acetone (1,200 c.c.); after the mixture had been stirred with anhydrous potassium carbonate (170 g., 1·2 mols.) until neutral (3 hours), ethyl sulphate (162 g., 1·05 mols.) was added slowly with vigorous stirring. The mixture soon solidified and it was necessary to break up the mass with a glass rod. The mixture was then boiled under reflux for 1 hour. The acetone was distilled off, finally under reduced pressure, water added, and the mixture stirred to hydrolyse unchanged ethyl sulphate. The mixture was acidified with concentrated hydrochloric acid (150 c.c.), and the ethanethiol evolved burned in a current of coal gas. The solution was extracted with carbon tetrachloride, and the organic layer washed with aqueous potassium carbonate and dried. The crude product after evaporation of the solvent was washed with light petroleum (b. p. 40—60°) and crystallised twice from the same solvent. The yield of 2-thio-5 : 5-dimethyl-3-ethyloxazolid-4-one thus obtained was 70 g. (40%). The potassium carbonate washings were acidified and 5 : 5-dimethyloxazolid-2 : 4-dione was isolated with the aid of ether.

When the ethylation was carried out in commercial dioxan by the following procedure, 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione was obtained. 2-Thio-5 : 5-dimethyloxazolid-4-one (72·5 g., 0·5 mol.) was dissolved in dioxan (300 c.c.), and ethyl sulphate (78 g., 0·51 mol.) was added with stirring. The mixture was boiled under reflux for 4½ hours at a bath temperature of 115°. Anhydrous potassium carbonate (166 g., 1·2 mols.) was added to the cooled solution, and the mixture warmed slowly to the b. p. under reflux, whereupon ethanethiol was evolved. Ethyl sulphate (78 g., 0·51 mol.) was then added dropwise at the b. p. during 1 hour, and boiling continued for 5 hours. The solvent was then distilled, finally under reduced pressure, and water (200 c.c.) and carbon tetrachloride (50 c.c.) were added. After the mixture had been stirred overnight, concentrated hydrochloric acid (150 c.c.) was added, and a further addition of water (350 c.c.) was necessary to dissolve inorganic salts. The organic layer was separated and the aqueous layer extracted 3 times with carbon tetrachloride. The combined extracts were washed with aqueous ammonia (2N.) and dried (Na_2SO_4). Evaporation yielded a brown oil which partly crystallised and gave 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione (41·1 g.; 52%) having m. p. and mixed m. p. with an authentic specimen, 76—77°.

When the ethylation was carried out by heating equimolecular quantities of the thio-oxazolidone and ethyl sulphate for ½ hour at 100—110° (bath temperature), little reaction taking place at 80°; 60% of 5 : 5-dimethyloxazolid-2 : 4-dione and about 5% of 5 : 5-dimethyl-3-ethyloxazolid-2 : 4-dione were isolated after acidification with hydrochloric acid.

2-Thio-3 : 5 : 5-trimethyloxazolid-4-one.—2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) was dissolved in a solution of sodium ethoxide obtained from sodium (4·6 g., 0·2 mol.) and dry ethanol (100 c.c.), and treated dropwise with methyl sulphate (25·2 g., 0·2 mol.). The mixture was boiled under reflux for 1 hour, the alcohol distilled, and the residue stirred with a slight excess of dilute hydrochloric acid; methanethiol was evolved. The product was extracted with ether, the solution washed with aqueous sodium hydrogen carbonate, the solvent distilled, and the residue fractionated. The fraction, b. p. 100—105°/8 mm., was crystallised from aqueous methanol and gave *2-thio-3 : 5 : 5-trimethyloxazolid-4-one* (21%) as colourless, glistening plates, m. p. 54—55° (Found: C, 45·9; H, 5·9; S, 19·6. $C_6H_9O_2NS$ requires C, 45·3; H, 5·7; S, 20·1%). With potassium ethoxide (0·2 mol.) in place of sodium ethoxide, the yield was 27%, and with no alkali present only partial *S*-methylation occurred.

Desulphurisation of the thio-oxazolidone with chlorine or bromine water gave an almost quantitative yield of 3 : 5 : 5-trimethyloxazolid-2 : 4-dione, m. p. and mixed m. p. with an authentic specimen, 45—46°. Desulphurisation with permanganate was carried out as follows. 2-Thio-3 : 5 : 5-trimethyloxazolid-4-one (31·8 g.) was suspended in water (25 c.c.), and a warm solution of potassium permanganate in sulphuric acid (2N.), saturated at 50°, added in portions with stirring until the solution exhibited a permanent pink colour. The solution was then treated with sulphur dioxide to dissolve oxides of manganese, saturated with salt, and extracted with ether. Evaporation of the dried ethereal solution, followed by cooling to −10°, gave 3 : 5 : 5-trimethyloxazolid-2 : 4-dione in almost quantitative yield.

Methylation of 2-Thio-5 : 5-dimethyloxazolid-4-one in Other Solvents.—(a) *In water.* A solution of the thio-oxazolidone (1 mol.) in an aqueous solution of the alkaline reagent (see below) was cooled in ice, and methyl sulphate (1·5 mols.) was added dropwise with vigorous stirring. Stirring was continued for 24 hours and the solution then made acid to Congo-red with hydrochloric acid. Sufficient carbon tetrachloride to dissolve the precipitated organic solid was added and stirring continued for 2 hours. The solution was then made alkaline with aqueous sodium hydrogen carbonate, and after being stirred for 1 hour the carbon tetrachloride layer was separated, washed with fresh aqueous sodium hydrogen carbonate, dried and distilled. The *N*-methylation product, 2-thio-3 : 5 : 5-trimethyloxazolid-4-one, b. p. 100—105°/8 mm., was collected. 5 : 5-Dimethyloxazolid-2 : 4-dione, formed by decomposition of the *S*-methylation product, was isolated from the acidified mother-liquors and washings by ether-extraction.

The percentages of *N*- and *S*-methylation occurring in aqueous solution with the use of various alkaline reagents are given in the following table.

Alkaline reagent.	*N*-Methyltion, %.	*S*-Methylation, %.	Alkaline reagent.	*N*-Methylation, %.	*S*-Methylation, %.
KOH (1 mol.)	18	64	K_2CO_3 (1·5 mols.)	28	60
*KOH (3 mols.)	4	—	K_2CO_3 (3 mols.)	31	56
$KHCO_3$ (3 mols.)	22	60	Na_2CO_3 (3 mols.)	20	65

* The bulk of the product was decomposed by the strong alkali.

(b) *In acetone and benzene.* A solution of the thio-oxazolidone (1 mol.) was stirred with the alkaline reagent (see below) for 2—3 hours to allow the alkali-metal salt to be formed, and methyl sulphate (1·25 mols.) added dropwise to the resulting suspension. The mixture was boiled under reflux for 3 hours, the solvent distilled, and the residue treated with dilute hydrochloric acid and worked up as for methylation in water. In acetone, a lower-boiling by-product, probably *acetone dimethyl mercaptol*, b. p. 56°/17 mm., was obtained (Found: C, 44·1; H, 8·6. $C_5H_{12}S_2$ requires C, 44·1; H, 8·8%).

The amount of *N*-methylation occurring is given in the following table:

Solvent.	Alkaline reagent.	*N*-Methylation, %.	Solvent.	Alkaline reagent.	*N*-Methylation, %.
Acetone	Na_2CO_3 (2 mols.)	31	Benzene ...	K_2CO_3 (2 mols.)	20
	K_2CO_3 (2 mols.)	44		None.	Partial *S*-methylation, only.
	$Ba(OH)_2$–Ba_2CO_3	49			

In the experiment with barium hydroxide and barium carbonate, the solution of the thio-oxazolidone was first stirred with an excess of barium hydroxide and then filtered, and methyl sulphate was added to the filtrate in presence of excess of barium carbonate.

2-Thio-3-benzyl-5 : 5-dimethyloxazolid-4-one.—A mixture of 2-thio-5 : 5-dimethyloxazolid-4-one (48 g., 0·33 mol.) in acetone (200 c.c.) and anhydrous potassium carbonate (60 g., 0·43 mol.) was stirred for 2 hours. Benzyl bromide (65 g., 0·38 mol.) was added and the mixture boiled under reflux for 1½ hours. Acetone was distilled off, and the residue stirred with water (150 c.c.) and carbon tetrachloride (200 c.c.). The organic layer was separated, washed with water, and stirred with warm hydrochloric acid (200 c.c.; 2N.), then washed in turn with water and aqueous ammonia (2N.), dried, and distilled. The fraction, b. p. 174—185°/5 mm., on storage and cooling deposited crystals, m. p. 81—85°. Repeated crystallisation from ether furnished a small quantity of *2-thio-3-benzyl-5 : 5-dimethyloxazolid-4-one*, m. p. 88—89° (Found: C, 61·2; H, 5·8. $C_{12}H_{13}O_2NS$ requires C, 61·25; H, 5·5%).

Under the following conditions of benzylation, 3-benzyl-5 : 5-dimethyloxazolid-2 : 4-dione was the only product obtained pure. 2-Thio-5 : 5-dimethyloxazolid-4-one (29 g., 0·2 mol.) in acetone (120 c.c.) was stirred with anhydrous potassium carbonate (44 g., 0·32 mol.) for 2 hours to form the potassium salt, benzyl chloride (35·5 g., 0·3 mol.) was added, and the mixture was boiled under reflux for 14 hours. After removal of the acetone, water (100 c.c.) and then concentrated hydrochloric acid (100 c.c.) were added, and the mixture was extracted with carbon tetrachloride. The extract was washed with aqueous ammonia (4N.), to remove 5 : 5-dimethyloxazolid-2 : 4-dione, and dried and the solvent distilled. The first fraction, b. p. 94—96°/30 mm., containing toluene-ω-thiol and related products, was discarded. The second fraction, a yellow oil, b. p. 164—180°/15 mm., when mixed with ether and light petroleum and cooled gave 3-benzyl-5 : 5-dimethyloxazolid-2 : 4-dione (5·15 g.), which after crystallisation from light petroleum (b. p. 60—80°) had m. p. 56—57° and did not depress the m. p. of an authentic specimen, m. p. 60—61°. Its constitution was confirmed on attempted de-sulphurisation with chlorine water; it was recovered unchanged.

British Schering Research Institute,
Alderley Edge, Cheshire.

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11. *Potential Trypanocides of the* N-*Heterocyclic Series. Part II. Analogues of Dimidium Bromide.*

By L. P. Walls and N. Whittaker.

The synthesis of analogues of dimidium bromide (III; R = Ph), in which the 9-phenyl group is replaced by a *cyclo*hexyl, benzyl, or heteromonocyclic nucleus, has been investigated for correlation of structure with trypanocidal activity. The phenanthridines (II) were readily obtained, but for steric reasons the *cyclo*hexyl compound did not give a quaternary salt. The furyl compound (II*b*) decomposed when treated with methyl sulphate, and the pyridylphenanthridine (II*c*) yielded a pyridinium salt when treated with methyl iodide or methyl sulphate. The benzyl- and 2-thienyl-phenanthridines (II) were converted into phenanthridinium salts, hydrolysis of which gave respectively highly effective trypanocides of type (III). The dihydropyranylphenanthridine (II*d*) could be quaternised, but an attempt to hydrolyse the urethane groups of the salt led to decomposition.

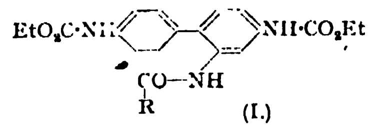
2 : 7-Diamino-9-*p*-aminophenyl-10-methylphenanthridinium chloride (III; R = *p*-$NH_2\cdot C_6H_4$, A = Cl) and its precursor (III; R = *p*-$NO_2\cdot C_6H_4$, A = Cl) are valuable trypanocides, the former being the most active phenanthridinium compound (*T. congolense* and *T. rhodesiense*) investigated to date. The triamino-salt was also obtained by an alternative synthesis.

The most active trypanocide of the phenanthridine series yet described is dimidium bromide (III; R = Ph), and it was early suggested (*J.*, 1945, 296) that its activity might be associated in part with the 2 : 7-arrangement of the amino-groups. The molecule contains a benzidine structure and it is well known that derivatives of benzidine are substantive towards vegetable fibres, and that a similar substantivity is frequently a property of trypanocidal drugs. It was desirable to test this hypothesis further by preparing other compounds of the series, which preserve the benzidine structure, but differ in the nature of the 9-substituent. The first compound of this type (III; R = Me) (*J.*, 1947, 68) to be tested is a much less effective trypanocide than dimidium bromide, but this may be the consequence of metabolism rather than of a reduced intrinsic trypanocidal activity. Compounds of the "Sontochin" type, which contain a 3-methylquinoline nucleus, are valuable antimalarials, but analogous compounds with a quinaldine nucleus are inactive and this striking difference is perhaps caused by the presence of the reactive α-methyl group, which may act as a focus for metabolic attack (Walker, *J.*, 1947, 1553). In the phenanthridine series the 9-methyl group is similarly highly reactive.

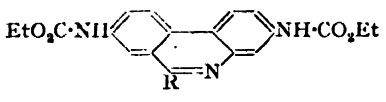
The 9-*cyclo*hexyl compound differs little from dimidium bromide in fundamental structure and for this reason its synthesis was attempted. *cyclo*Hexanecarboxyl chloride and 2-amino-4 : 4′-biscarbethoxyaminodiphenyl in pyridine furnished a good yield of the *amide* (I; R = C_6H_{11}), which was cyclised by phosphoryl chloride to *2 : 7-biscarbethoxyamino-*9-cyclo*hexylphenanthridine* (II; R = C_6H_{11}). A quaternary salt could not be obtained from this substance: treatment with nitrobenzene–methyl sulphate at 170° and cooling gave the *sulphate* of the base, but with methyl toluene-*p*-sulphonate no reaction occurred. Even with carefully purified methyl sulphate alone, some sulphate was formed. This experience recalls the similar product obtained from 6-acetamido-2-*p*-aminostyrylquinoline by Browning, Cohen, Cooper, and Gulbransen (*Proc. Roy. Soc.*, B, 1931, 109, 53), which may very likely have been a sulphate rather than the postulated complex with methyl sulphate. The failure of the *cyclo*hexyl compound to yield quaternary salts is explicable by steric hindrance: models reveal that the *cyclo*hexyl group offers much more obstruction to accommodation of a methyl group on $N_{(10)}$ than does a phenyl group.

With (III; R = CH_2Ph) an intermediate type between dimidium bromide and (III; R = Me) is under consideration; the methylene group might likewise be regarded as a point of metabolic attack but oxidation of the benzyl compound is less likely to involve the loss of the essential quaternary system. However, 7-amino-9-*p*-aminobenzyl-10-methylphenanthridinium bromide is very much less active than the corresponding *p*-aminophenyl compound (Part I). Condensation of 2-amino-4 : 4'-biscarbethoxyaminodiphenyl and phenylacetyl chloride afforded *2-phenylacetamido-4 : 4'-biscarbethoxyaminodiphenyl* (I; R = CH_2Ph) which was smoothly cyclised to *2 : 7-biscarbethoxyamino-9-benzylphenanthridine* (II; R = CH_2Ph); successive quaternisation and hydrolysis converted this compound into the desired salt (III; R = CH_2Ph, A = Br), which is highly trypanocidal (*Trypanosoma congolense*) although less effective than dimidium bromide.

The effect of replacement of the 9-phenyl group of dimidium bromide by heterocyclic nuclei was also examined, readily accessible nuclei of widely different type being used, namely 2-thienyl, 5-nitro-2-furyl, 3-pyridyl, and 5 : 6-dihydro-3-pyranyl. 2-Acetylthiophen was oxidised by sodium hypochlorite to thiophen-2-carboxylic acid and the derived chloride was condensed with 2-amino-4 : 4'-biscarbethoxyaminodiphenyl to yield *2-(thiophene-2''-carboxyamido)-4 : 4'-biscarbethoxyaminodiphenyl* (I*a*). Cyclisation then furnished *2 : 7-biscarbethoxyamino-9-2'-thienylphenanthridine* (II*a*), and this was converted by the customary methods into the quaternary salt (III; R = 2-thienyl, A = Br), which is a more effective trypanocide (*T. congolense*) than dimidium bromide. The 5-nitro-2-furyl nucleus has already been associated with biologically active compounds: furacin (5-nitro-2-furaldehyde semicarbazone) is an effective antibacterial and as a trypanocide (Dodd and Stillman, *J. Pharm. Exp. Ther.*, 1944, **82**, 11). 5-Nitro-2-furoic acid led, as above, to *2 : 7-biscarbethoxyamino-9-(5-nitro-2-furyl)phenanthridine* (II*b*), but attempts to form quaternary salts caused profound decomposition.

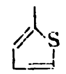


(I.)

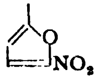


(II.)

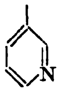
R = (*a*)



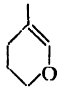
(*b*)

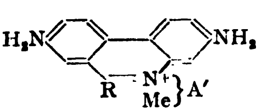


(*c*)

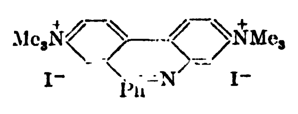


(*d*)

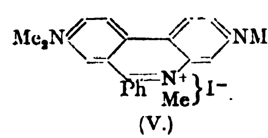




(III.)



(IV.)



(V.)

Petrow and Wragg (*J.*, 1947, 1410) have reported that the synthesis of 9-pyridylphenanthridines from 2-nicotinamidodiphenyls may result in low yields, even after prolonged heating with nitrobenzene–phosphoryl chloride. In the initial reaction between the amide and phosphoryl chloride, hydrogen chloride is liberated and thus a proton becomes bound to the pyridine-N. The inductive effect of this positive pole appears to decrease the electrophilic affinity of the amide-C atom and hence retards cyclisation (ring-closure being an electrophilic-substitution reaction). However, in accordance with our experience of *o*-acylamidodiphenyls with urethane substituents, cyclisation of *2-nicotinamido-4 : 4'-biscarbethoxyaminodiphenyl* (I*c*) proceeded under milder conditions, although the yield of the *phenanthridine* (II*c*) was rather low (25%). Under similar conditions the *methochloride* of the foregoing amide was recovered unchanged, in confirmation of the retarding effect on ring-closure of a positive pole in the acyl group. With methyl sulphate in nitrobenzene at 135°, or preferably with methyl iodide in refluxing dioxan, the pyridylphenanthridine gave a gum from which, by addition of an excess of aqueous naphthalene-β-sulphonic acid, a colourless, *1'-methonaphthalene-β-sulphonate 10-naphthalene-β-sulphonate* was obtained. This salt, when treated with aqueous sodium acetate, gave a yellow *methonaphthalene-β-sulphonate* and it is certain that this was the pyridinium salt (Petrow and Wragg, *loc. cit.*) and not the phenanthridinium salt; since attempts at hydrolysis of the urethane groups did not lead to crystalline products, the series was not examined further. To complete the investigation with 9-heterocyclic substituents, 5 : 6-dihydropyran-3-carboxyl chloride (B.P. 570,974) was condensed with 2-amino-4 : 4′-biscarbethoxyaminodiphenyl and the resultant *amide* (I*d*) cyclised to 2 : 7-*biscarbethoxyamino*-9-(5 : 6-*dihydro*-3-*pyranyl*)*phenanthridine* (II*d*). Treatment of this compound with methyl sulphate, followed by metathesis with dilute hydrochloric acid, yielded a yellow *methochloride* but it was not possible to convert this into the diamino-quaternary salt since acid hydrolysis also affected the dihydropyran ring (Schniepp and Geller, *J. Amer. Chem. Soc.*, 1946, **68**, 1646).

A new approach to the production of more active trypanocides followed from the following considerations. 9-Phenyl-10-methylphenanthridinium chloride itself exhibits slight trypanocidal activity; with an amino-substituent in the diphenyl portion of the molecule this activity becomes significant, and reaches a high level with two such substituents (as in dimidium bromide), although one of the two amino-groups may then be located in the 9-phenyl group (*J.*, 1945, 297). It was of interest therefore to examine whether a third amino-group would further enhance the therapeutic effect. 2-p-*Nitrobenzamido*-4 : 4′-*biscarbethoxyaminodiphenyl* (I; R = p-$NO_2 \cdot C_6H_4$) was cyclised to 2 : 7-*biscarbethoxyamino*-9-p-*nitrophenylphenanthridine* (II; R = p-$NO_2 \cdot C_6H_4$) by phosphoryl chloride. This reacted readily in nitrobenzene with methyl sulphate to give the quaternary *methosulphate*, which afforded a good yield of 2 : 7-*diamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride* (III; R = p-$NO_2 \cdot C_6H_4$, A = Cl) when hydrolysed with sulphuric acid (*d* 1·66) at 125—130°. If the reaction temperature was increased to 150—155° some loss of the quaternary group occurred concurrently with hydrolysis of the urethane groups. Reduction of (III; R = p-$NO_2 \cdot C_6H_4$, A = Cl) with iron powder and water was unsatisfactory, and the method was not applicable to the corresponding *nitro-diacetamido*-salt. During an examination of numerous reducing agents, however, it was found that heating this salt in water with a 30% excess of ferrous hydroxide (prepared from stoicheiometric quantities of ferrous sulphate and barium hydroxide) gave the *amino-diacetamido*-salt almost quantitatively, and from this 2 : 7-*diamino*-9-p-*aminophenyl*-10-*methylphenanthridinium chloride* (III; R = p-$NH_2 \cdot C_6H_4$, A = Cl) was readily obtained by dilute hydrochloric acid. Similarly, by reduction with ferrous hydroxide (a method better suited to nitro-quaternary salts in general than is iron powder, a cleaner product being obtained), the salt (III; R = p-$NO_2 \cdot C_6H_4$, A = Cl) was converted directly and quantitatively into the *triamino*-salt (III; R = p-$NH_2 \cdot C_6H_4$, A = Cl). Both the nitro-diamino- and triamino-salts are highly trypanocidal, the former being at least equal to dimidium bromide in *T. congolense* infections in mice and dogs, and the latter markedly more active and somewhat less (acutely) toxic. The triamino-salt is also highly active in *T. rhodesiense* infections in mice; in this respect it much exceeds any other phenanthridinium compound yet investigated, being as active as pentamidine although more toxic. None of the compounds here described has a prophylactic action against trypanosomes comparable with that of pentamidine. In an alternative route to the triamino-salt, 4 : 4′-*dinitro*-2-p-*nitrobenzamidodiphenyl* was converted into 2 : 7-*dinitro*-9-p-*nitrophenylphenanthridine* which, unlike dinitro-compounds of the same type, did not yield quaternary salts. The corresponding *triamino*-compound, which is devoid of trypanocidal activity, was converted into the *triacetyl* derivative from which a quaternary *methosulphate* was obtained in rather poor yield. This salt was hydrolysed by dilute acid to the triamino-salt (III; R = p-$NH_2 \cdot C_6H_4$, A = Cl).

By methods similar to those already described, 4 : 4′-*biscarbethoxyamino*-2-p-*anisoamidodiphenyl* (I; R = p-$MeO \cdot C_6H_4$) was converted into 2 : 7-*biscarbethoxyamino*-9-p-*methoxyphenylphenanthridine* (II; R = p-$MeO \cdot C_6H_4$) and its *methosulphate*, but the product of hydrolysis of the latter, although undoubtedly containing salts of the type (III), could not be obtained crystalline owing, it is believed, to some simultaneous hydrolysis of the methoxyl group.

Modification of dimidium bromide in a different way was effected as follows. Methylation of 2 : 7-diamino-9-phenylphenanthridine (*J.*, 1945, 299) in aqueous methanol by methyl iodide in the presence of sodium carbonate furnished the white bisquaternary *iodide* (IV) in good yield. Pyrolysis of this salt at 180° caused loss of one mole of methyl iodide and formation of 2 : 7-*bisdimethylamino*-9-*phenyl*-10-*methylphenanthridinium iodide* (V). The corresponding *bromide* is a purple salt, bluer in tint than dimidium bromide, possessing the high antibacterial activity *in vitro* characteristic of phenanthridinium salts, but both this and (V) are practically inactive against trypanosomes. This result suggests that hydrogen-bonding, or some other reaction between drug and substrate not possible with a tertiary amine, is associated with the trypanocidal action of dimidium bromide and its analogues.

EXPERIMENTAL.

(All the products were dried to constant weight before analysis.)

2-cyclo*Hexanecarboxyamido-4 : 4′-biscarbethoxyaminodiphenyl* (I; R = C_6H_{11}).—*cyclo*Hexanecarboxyl chloride (26 g.) was added to a suspension of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (52 g.) in dry pyridine (75 ml.), and the mixture heated on the steam-bath for 15 minutes and then poured into water (2 l.). The oil which separated soon solidified and, when crystallised from alcohol, formed colourless needles (63 g.) of the *amide*, m. p. 184—185° (Found: C, 66·1; H, 6·75; N, 9·5. $C_{25}H_{31}O_5N_3$ requires C, 66·2; H, 6·85; N, 9·25%).

2 : 7-*Biscarbethoxyamino*-9-cyclo*hexylphenanthridine* (II; R = C_6H_{11}).—The amide (I; R = C_6H_{11}) (63 g.) and phosphoryl chloride (63 ml.) were heated at 130° (bath) for 45 minutes. At the outset there was vigorous evolution of hydrogen chloride, and after 15 minutes a yellow solid began to crystallise. The reaction mixture was stirred with ice and an excess of ammonia for a time, then boiled for a few minutes, and cooled, and the aqueous liquor decanted from the rock-like solid. On being heated with alcohol containing a few ml. of concentrated ammonia solution, this solid gave place to colourless prisms which, after cooling, were collected and washed with water and alcohol. The product, 2 : 7-*biscarbethoxyamino*-9-cyclo*hexylphenanthridine* (55 g.), had m. p. 233—234°, unchanged on recrystallisation from alcohol–acetone (Found: C, 69·1; H, 6·65; N, 9·55. $C_{25}H_{29}O_4N_3$ requires C, 68·95; H, 6·65; N, 9·65%). This compound (2 g.), dissolved in nitrobenzene (15 ml.), was treated with methyl sulphate (1·2 ml.) at 170° for 10 minutes. On cooling, a yellow crystalline substance slowly separated, which was not the quaternary salt, for it was hydrolysed by 2N-sodium acetate to the starting material. It crystallised from methanol in small yellow needles, m. p. 227—228° (decomp.), and proved to be the *hydrogen sulphate* of the original base (Found: C, 55·5; H, 5·65; N, 7·8; S, 5·8. $C_{25}H_{29}O_4N_3,H_2SO_4$ requires C, 56·25; H, 5·8; N, 7·85; S, 6·0%). The same substance was immediately precipitated on addition of sulphuric acid to a hot nitrobenzene solution of the base.

2-*Phenylacetamido-4 : 4′-biscarbethoxyaminodiphenyl* (I; R = CH_2Ph).—Phenylacetyl chloride (5·5 g.) was added to a hot suspension of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (12 g.) in chlorobenzene (130 ml.), and the mixture refluxed gently for 30 minutes. On cooling, the pure *amide* crystallised as colourless needles (15·1 g.), m. p. 204—205°, unchanged by recrystallisation from alcohol (Found: C, 68·2; H, 5·95; N, 9·15. $C_{26}H_{27}O_5N_3$ requires C, 67·65; H, 5·9; N, 9·1%).

2 : 7-*Biscarbethoxyamino-9-benzylphenanthridine* (II; R = CH_2Ph).—The amide (I; R = CH_2Ph) (13·2 g.) and phosphoryl chloride (40 ml.) were refluxed for 1 hour, cooled, and poured into water. After cooling, the deep-yellow solid was collected and dissolved in pyridine, and the solution diluted with water; the precipitate formed was washed thoroughly with water, followed by methanol. The *phenanthridine* (11·4 g.) had m. p. 255° (decomp.) raised to 259° (decomp.) by recrystallisation from acetone or aqueous pyridine (Found: C, 70·55; H, 5·45; N, 9·5. $C_{26}H_{25}O_4N_3$ requires C, 70·4; H, 5·7; N, 9·5%).

Methyl sulphate (10 ml.) was added to a solution of this base (10 g.) in nitrobenzene (80 ml.) at 170°, and the temperature maintained at 160—165° for 3 minutes. The yellow solid, which crystallised out rapidly on cooling, was collected, washed with benzene, dried, and extracted with boiling water. Addition of 2N-hydrochloric acid to the filtered aqueous solution precipitated the *methochloride* (7·2 g.), m. p. 253° (decomp.), which crystallised from methanol in small bright yellow blades, m. p. 254° (decomp.) (Found: N, 8·35; Cl, 7·15. $C_{27}H_{28}O_4N_3Cl$ requires N, 8·5; Cl, 7·2%).

2 : 7-*Diamino-9-benzyl-10-methylphenanthridinium Bromide* (III; R = CH_2Ph, A = Br).—The foregoing methochloride (7·9 g.), concentrated sulphuric acid (28 ml.), and water (24 ml.) were heated at 150° until effervescence ceased (*ca.* 30 minutes), and then poured into water, and the red solution was carefully neutralised with aqueous ammonia. The gum which separated readily solidified; it was dissolved in water, and the filtered solution treated with potassium bromide to precipitate 2 : 7-*diamino-9-benzyl-10-methylphenanthridinium bromide* (5·8 g.) as a hydrate of indefinite m. p. Crystallisation from methanol yielded purple needles, m. p. 250—252° (Found: N, 10·65; Br, 20·1. $C_{21}H_{20}N_3Br$ requires N, 10·65; Br, 20·3%).

Thiophen-2-carboxylic Acid.—2-Acetylthiophen (60 g.) (prepared according to Hartough and Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 1012) was covered with 10% sodium hypochlorite solution (500 g.) and vigorously stirred on the steam-bath. A vigorous reaction ensued and chloroform was evolved. Heating was then discontinued and, when the reaction had subsided, more hypochlorite solution was added in portions of 50 g. until chloroform was no longer evolved. After cooling of the mixture a slight excess of liquid sulphur dioxide was added, and the solution acidified with sulphuric acid and extracted with ether. The extract was shaken with sodium hydroxide solution, and the aqueous layer separated and aerated until all traces of ether were removed. Acidification with sulphuric acid precipitated thiophen-2-carboxylic acid (45—50 g.), m. p. 124—125°.

2′′-(*Thiophen-2-carboxyamido*)-4 : 4′-*biscarbethoxyaminodiphenyl* (I*a*).—A mixture of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (70·5 g.), nitrobenzene (300 ml.), and thiophen-2-carboxyl chloride (30 g.) was heated in a bath at 150° for 2 hours, and the solution left overnight. The crystalline product was collected, washed with nitrobenzene, treated with hot alcohol (300 ml.), and heated for a few minutes. On cooling, the pure *amide* separated as dense colourless prisms (79 g.), m. p. 197—198°, unchanged on recrystallisation from " Cellosolve " (Found: N, 9·3; S, 7·3. $C_{23}H_{23}O_5N_3S$ requires N, 9·25; S, 7·05%).

2 : 7-*Biscarbethoxyamino-9-2′-thienylphenanthridine* (II*a*).—The amide (I*a*) (79 g.) and phosphoryl chloride (80 ml.) were heated at 130—135° (bath) for 75 minutes, cooled, poured on ice, and neutralised with aqueous ammonia. The solid product was dissolved in hot pyridine, diluted with water, and cooled, and small quantities of glacial acetic acid were added with stirring until the oil solidified. A solution of this material in hot glacial acetic acid (400 ml.) was treated with concentrated hydrochloric acid (40 ml.) and, after cooling, the red needles were collected and recrystallised from glacial acetic acid. The hydrochloride thus obtained was dissolved in hot alcohol, and neutralised with the minimum quantity of concentrated aqueous ammonia (until the red colour had given place to yellow), and a seed of the product was introduced. Almost immediately the *phenanthridine* separated as pale yellow prisms (35 g.),

m. p. 227—229° (decomp.), raised to 229—230° (decomp.) on recrystallisation from alcohol–acetone (Found : N, 9·75; S 7·4. $C_{22}H_{21}O_4N_3S$ requires N 9·65; S 7·35%).

2 : 7-*Biscarbethoxyamino*-9-2′-*thienyl*-10-*methylphenanthridinium Chloride.*—To (II*a*) (16 g.) in nitrobenzene (80 ml.) at 120°, methyl sulphate (24 ml.) was added. The mixture was heated to 135° and then cooled immediately. The orange plates (18 g.) that separated were washed with benzene and dissolved in hot water, and concentrated hydrochloric acid was added to precipitate the *methochloride*, which crystallised from water containing a few drops of 2N-hydrochloric acid, in fine orange needles (16 g.), m. p. 239° (decomp.) (Found : N, 8·7; S, 6·95; Cl, 7·4. $C_{24}H_{24}O_4N_3ClS$ requires N, 8·65; S 6·6; Cl, 7·3%).

2 : 7-*Diamino*-9-2′-*thienyl*-10-*methylphenanthridinium bromide* (III; R = 2-thienyl, A = Br) was obtained by hydrolysis of the foregoing methochloride (11·5 g.) with aqueous sulphuric acid (*d* 1·53) at 135—140°. From a solution of the crude bromide in hot alcohol a mixture of black needles and a fine crystalline precipitate separated with cooling, of which only the former were soluble in cold water. An aqueous extract was treated with potassium bromide, and the precipitated material crystallised from alcohol in deep-purple prisms and needles of 2 : 7-diamino-9-2′-thienyl-10-methylphenanthridinium bromide (5·6 g.), m. p. 256° (decomp.) (Found : N, 10·9; S, 8·3; Br, 20·5. $C_{18}H_{16}N_3SBr$ requires N, 10·85; S, 8·3; Br, 20·7%).

2-(5-*Nitro*-2-*furoamido*)-4 : 4′-*biscarbethoxyaminodiphenyl* (I*b*).—This *amide* was the product of condensation of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (75 g.) and 5-nitro-2-furoyl chloride (39 g.) in dry pyridine (150 ml.); it crystallised from glacial acetic acid in yellowish-brown prisms (95 g.), m. p. 223—225° (Found : C, 57·0; H, 4·45; N, 11·85. $C_{23}H_{22}O_8N_4$ requires C, 57·25; H, 4·55; N, 11·6%).

2 : 7-*Biscarbethoxyamino*-9-(5-*nitro*-2-*furyl*)*phenanthridine* (II*b*).—The amide (I*b*) (95 g.) was cyclised with phosphoryl chloride. The crude product was dissolved in hot pyridine, water added, and the precipitated black solid refluxed with glacial acetic acid (500 ml.) and cooled. The brown residue (18 g.), m. p. 275—277° (decomp.), was crystallised from pyridine, the *phenanthridine* separating as red prisms (15·5 g.) containing pyridine of crystallisation (11·5%); at 125° the prisms lost pyridine and became yellowish-brown, melting at 286—288° (decomp.) (Found : C, 59·6; H, 4·5; N, 12·15. $C_{23}H_{20}O_7N_4$ requires C, 59·5; H, 4·3; N, 12·05%).

2-*Nicotinamido*-4 : 4′-*biscarbethoxyaminodiphenyl* (I*c*).—2 Amino-4 : 4′-biscarbethoxyaminodiphenyl (27·5 g.) was treated with nicotinyl chloride hydrochloride [prepared from nicotinic acid (10 g.) and thionyl chloride] in dry pyridine (100 ml.). The reaction product gave, on being refluxed in alcohol (1000 ml.) and cooled, colourless prisms of the *amide* (27 g.), m. p. 228—229° (decomp.) unchanged on recrystallisation from "Cellosolve" (Found : C, 64·4; H, 5·45; N, 12·4. $C_{24}H_{24}O_5N_4$ requires C, 64·3; H, 5·35; N, 12·5%). The substance (5 g.) was heated with alcohol (25 ml.) containing methyl iodide (5 ml.) in a pressure bottle at 100° for 40 minutes, and then evaporated to dryness, and the residue extracted with hot water. From the filtered solution fine colourless needles (5·2 g.) of the *methiodide*, m. p. 159—161° (decomp.), of (I*c*) separated on cooling; when recrystallised from alcohol the needles had m. p. 162° (decomp.) (Found : N, 9·55; I, 21·35. $C_{25}H_{27}O_5N_4I$ requires N, 9·5; I, 21·55%).

2 : 7-*Biscarbethoxyamino*-9-3′-*pyridylphenanthridine* (II*c*).—(I*c*) (46 g.), phosphoryl chloride (46 ml.), and nitrobenzene (46 ml.) were heated at 130° (bath) for 1 hour and then poured on ice, and the nitrobenzene distilled with steam. On neutralisation of the aqueous residue with ammonia solution and cooling, an amorphous product (41 g.) was obtained, which was digested with hot 0·5N-hydrochloric acid (650 ml.) and left overnight. Unchanged amide (10 g.) was separated by centrifugation and washed with 0·5N-hydrochloric acid, and the aqueous liquors were heated with an excess of naphthalene-β-sulphonic acid. On cooling, colourless prisms (25 g.) separated, which were washed with aqueous naphthalene-β-sulphonic acid, suspended in water, and boiled for a few minutes with a slight excess of aqueous ammonia. The precipitate was extracted with cold 0·5N-hydrochloric acid (200 ml.), and the filtered solution neutralised with aqueous ammonia; the product (9 g.) was further purified by chromatography (Al_2O_3) in acetone solution, and crystallised from alcohol. 2 : 7-*Biscarbethoxyamino*-9-3′-*pyridylphenanthridine* was obtained as almost colourless prisms and needles (7·8 g.), m. p. 196—198° (decomp.) (Found : C, 66·8; H, 5·4; N, 12·9. $C_{24}H_{22}O_4N_4$ requires C, 66·95; H, 5·1; N, 13·0%).

2 : 7-*Biscarbethoxyamino*-9-3′-*pyridylphenanthridine* 1′-*Methonaphthalene*-β-*sulphonate.*—(II*c*) (10·6 g.), dioxan (50 ml.), and methyl iodide (11 ml.) were refluxed for 1 hour and then cooled, and the gum left after decantation dissolved in hot water (*ca.* 250 ml.) containing a few drops of glacial acetic acid. After cooling, the filtered solution was reheated, and an excess of naphthalene-β-sulphonic acid added to precipitate the 1′-*methonaphthalene*-β-*sulphonate* 10-*naphthalene*-β-*sulphonate*, which crystallised from methanol as colourless prisms (9·9 g.), m. p. 228—229° (decomp.) (Found : N, 6·45; S, 7·55. $C_{35}H_{32}O_7N_4S,C_{10}H_7{\cdot}SO_3H$ requires N, 6·5; S, 7·45%). When this substance was boiled with an excess of aqueous sodium acetate, the prisms gave place to yellow needles of the 1′-*methonaphthalene*-β-*sulphonate* which, after cooling, were collected, and recrystallised from alcohol in yellow prisms, m. p. 142° (decomp.) (Found : N, 8·7; S, 5·15. $C_{35}H_{32}O_7N_4S$ requires N, 8·6; S, 4·9%).

2-(5 : 6-*Dihydropyran*-3-*carboxyamido*)-4 : 4′-*biscarbethoxyaminodiphenyl* (I*d*).—This was prepared by reaction of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (24 g.) with 5 : 6-dihydropyran-3-carboxyl chloride (10·8 g.) in dry pyridine (50 ml.). After recrystallisation from alcohol, the *amide* (21·5 g.) had m. p. 186—188° (Found : C, 63·55; H, 5·55; N, 9·4. $C_{24}H_{27}O_6N_3$ requires C, 63·55; H, 5·95; N, 9·25%).

2 : 7-*Biscarbethoxyamino*-9-(5 : 6-*dihydro*-3-*pyranyl*)*phenanthridine* (II*d*).—Cyclisation of (I*d*) with phosphoryl chloride at 130° yielded a crude mixture from which the product was isolated as a hydrobromide and then converted into the free base by aqueous ammonia. Recrystallisation from alcohol–acetone afforded a 15% yield of the *phenanthridine* as colourless prisms, m. p. 215—216° (Found : C, 66·2; H, 5·8; N, 10·2. $C_{24}H_{25}O_5N_3$ requires C, 66·2; H, 5·75; N, 9·65%). The substance (3·5 g.) was heated in nitrobenzene with methyl sulphate at 135° for 5 minutes, and then poured into benzene. The precipitated solid gave, by metathesis with dilute hydrochloric acid (*ca.* 0·1N.), the *methochloride* (4·1 g.) as yellow needles, m. p. 256—258° (decomp.), raised to 260° (decomp.) on recrystallisation from water (Found : N, 9·0; Cl, 7·45. $C_{25}H_{28}O_5N_3Cl$ requires N, 8·65; Cl, 7·3%).

2 : 7-*Biscarbethoxyamino*-9-p-*nitrophenylphenanthridine* (II; R = *p*-$NO_2{\cdot}C_6H_4$).—2-Amino-4 : 4′-bis-

carbethoxyaminodiphenyl (69 g.) and *p*-nitrobenzoyl chloride (42 g.) were heated in nitrobenzene (280 ml.) at 150° for 30 minutes and then cooled, and the product that separated recrystallised from alcohol. 2-p-*Nitrobenzamido*-4 : 4′-*biscarbethoxyaminodiphenyl* (I; R = *p*-NO_2·C_6H_4) crystallised in yellow prisms (84 g.), m. p. 202° (Found : C, 60·85; H, 4·75; N, 11·45. $C_{25}H_{24}O_7N_4$ requires C, 60·95; H, 4·9; N, 11·4%). This substance (80 g.) was cyclised with phosphoryl chloride, the *phenanthridine* (46 g.) crystallising from pyridine in spherical aggregates of fine yellow needles, m. p. *ca.* 247° (decomp.) (Found : C, 63·2; H, 4·4; N, 11·75. $C_{25}H_{22}O_6N_4$ requires C, 63·3; H, 4·65; N, 11·8%).

2 : 7-*Diamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride* (III; R = *p*-NO_2·C_6H_4, A = Cl).—(II; R = *p*-NO_2·C_6H_4) (82 g.) was treated with methyl sulphate (70 ml.) in nitrobenzene solution (500 ml.) in the same manner as the corresponding thienyl compound. The orange solid obtained was refluxed with acetone (400 ml.) for a few minutes and then cooled, and the 2 : 7-*biscarbethoxyamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium methyl sulphate* (96 g.) (containing a small quantity of sulphate), m. p. *ca.* 238° (decomp.), collected. Recrystallisation from methanol yielded pure methosulphate as orange needles, m. p. *ca.* 240—241° (decomp.) (Found : C, 54·1; H, 4·45; N, 9·6; S, 5·35. $C_{27}H_{28}O_{10}N_4S$ requires C, 54·0; H, 4·65; N, 9·35; S, 5·35%). Hydrolysis of this substance (96 g.) with aqueous sulphuric acid (*d* 1·66) at 125—130° for 30 minutes, followed by metathesis of the product with sodium chloride, gave 2 : 7-*diamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride*, which crystallised from water in dark purple prisms (51·5 g.), m. p. *ca.* 235° (decomp.) (Found : C, 63·3; H, 4·25; N, 14·45; Cl, 9·25. $C_{20}H_{17}O_2N_4Cl$ requires C, 63·05; H, 4·45; N, 14·7; Cl, 9·35%).

2 : 7-*Diacetamido*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride*.—Acetic anhydride (10 ml.) was added to a hot suspension of (III; R = *p*-NO_2·C_6H_4; A = Cl) (5 g.) in glacial acetic acid (50 ml.), and the whole heated for 30 minutes on the steam-bath. The cooled product was collected and recrystallised from water as fine orange needles of the *nitro-diacetamido*-salt (4·7 g.), m. p. >300° (Found : N, 12·0; Cl, 7·35. $C_{24}H_{21}O_4N_4Cl$ requires N, 12·05; Cl, 7·65%).

2 : 7-*Diacetamido*-9-p-*aminophenyl*-10-*methylphenanthridinium Chloride*.—Solutions of ferrous sulphate heptahydrate (33 g.) and barium hydroxide octahydrate (36 g.) in hot water were mixed, and the resultant sludge added to a stirred suspension of the foregoing nitro-diacetamido-salt (7·5 g.) in water (1500 ml.) at 90—95°. After being heated on the steam-bath for 30 minutes, the mixture was filtered through a preheated funnel, and the residue washed with hot water. The aqueous filtrate was again heated to 90—95° and subjected to further interaction with ferrous hydroxide, prepared from ferrous sulphate (16·5 g.) and barium hydroxide (18 g.), for 30 minutes. The hot aqueous filtrate was treated with sodium chloride to precipitate the *amino-diacetamido*-salt, which crystallised from water in small yellow needles (6·1 g.), m. p. *ca.* 280—281° (decomp.) (Found : N, 12·8; Cl, 8·2. $C_{24}H_{23}O_2N_4Cl$ requires N, 12·9; Cl, 8·15%).

2 : 7-*Diamino*-9-p-*aminophenyl*-10-*methylphenanthridinium Chloride* (III; R = *p*-NH_2·C_6H_4, A = Cl).—(*a*) The amino-diacetamido-salt (6·05 g.) and 2N-hydrochloric acid (60 ml.) were refluxed for 1 hour, and the red solution was diluted with water (140 ml.) and neutralised carefully with aqueous ammonia; the separation of red prisms was completed by addition of sodium chloride. Recrystallisation from water (40 ml.) containing sodium chloride (0·5 g.) yielded dark red pyramids of the *triamino*-salt (4·7 g.), m. p. *ca.* 240° (decomp.) (Found : N, 16·0; Cl, 10·1. $C_{20}H_{19}N_4Cl$ requires N, 16·0; Cl, 10·15%).

(*b*) Reduction of (III; R = *p*-NO_2·C_6H_4, A = Cl) (30·5 g.) with ferrous hydroxide, prepared from ferrous sulphate (224 g.) and barium hydroxide (240 g.), according to the method just described, yielded a red aqueous solution which was concentrated to *ca.* 500 ml. Metathesis with sodium chloride gave red prisms which, on recrystallisation as in (*a*), yielded dark red pyramids of the same triamino-salt (26·2 g.), m. p. *ca.* 240° (decomp.).

(*c*) Equimolecular quantities of 4 : 4′-dinitro-2-aminodiphenyl and *p*-nitrobenzoyl chloride were condensed in boiling nitrobenzene. After evolution of hydrogen chloride had ceased, the solution was cooled to allow separation of 2-p-*nitrobenzamido*-4 : 4′-*dinitrodiphenyl* in almost quantitative yield. Recrystallisation from aqueous pyridine furnished small yellow prisms, m. p. 234° (Found : C, 56·2; H, 2·9; N, 13·75. $C_{19}H_{12}O_7N_4$ requires C, 55·85; H, 2·95; N, 13·7%). When this amide was refluxed in nitrobenzene–phosphoryl chloride for several hours (B.P. 520,273) 2 : 7-*dinitro*-9-p-*nitrophenylphenanthridine* crystallised almost quantitatively in cream-coloured needles; recrystallisation from nitrobenzene gave a product, m. p. 356—358° (Found : C, 58·6; H, 2·15; N, 14·35. $C_{19}H_{10}O_6N_4$ requires C, 58·45; H, 2·6; N, 14·35%). The foregoing powdered trinitro-compound (5 g.) was suspended in alcohol (125 ml.), concentrated hydrochloric acid (25 ml.) and crystalline stannous chloride (30 g.) were added, and the mixture was refluxed for 2 hours. After cooling, the dark red solid was collected, dissolved in hot water, separated from unchanged trinitro-compound (1·1 g.), and then stirred into excess of sodium hydroxide solution. 2 : 7-*Diamino*-9-p-*aminophenylphenanthridine* was thus precipitated as a yellow solid, which crystallised from alcohol in yellow plates, m. p. 246° (Found : C, 76·0; H, 5·45; N, 18·35. $C_{19}H_{16}N_4$ requires C, 76·0; H, 5·35; N, 18·65%). This base was extremely soluble in dilute acid, affording intense carmine solutions. It was acetylated by acetic anhydride–acetic acid; on dilution of the solution thus obtained with water an orange gel formed, which was converted into a flocculent precipitate by the addition of aqueous ammonia. Crystallisation of this product from alcohol afforded 2 : 7-*diacetamido*-9-p-*acetamidophenylphenanthridine* in cream-coloured wool-like needles, m. p. 312° (Found : C, 69·9; H, 5·65; N, 13·25. $C_{25}H_{22}O_3N_4$ requires C, 70·4; H, 5·2; N, 13·15%). A suspension of this compound (5 g.) in nitrobenzene (150 ml.) at 180° was treated with methyl sulphate (5 g.). The gum that separated was isolated by decantation and refluxed with alcohol (200 ml.). The 2 : 7 : 4′-*triacetamido*-9-*phenyl*-10-*methylphenanthridinium sulphate* thus left undissolved crystallised from methanol in orange plates (2 g.), m. p. 248° (decomp.) [Found : C, 63·95; H, 5·35; N, 11·05. $(C_{26}H_{25}O_3N_4)_2SO_4$ requires C, 63·8; H, 5·15; N, 11·45%]. Hydrolysis of this salt could be affected by refluxing it with N-hydrochloric acid until a clear solution was obtained (several days); more conveniently and with less serious bumping the salt (0·4 g.) was heated in suspension in 10% methanolic hydrochloric acid (15 ml.) until all had dissolved (*ca.* 6 hours), the solution being then evaporated to small bulk. When the residue was neutralised with aqueous ammonia the triamino-salt separated and was purified as in (*a*) (Found : N, 15·5; Cl, 10·1%).

2 : 7-*Biscarbethoxyamino-9-*p-*methoxyphenylphenanthridine* (II; R = *p*-MeO·C_6H_4).—Condensation of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl and *p*-anisoyl chloride in boiling chlorobenzene furnished 2-p-*anisamido-4 : 4′-biscarbethoxyaminodiphenyl* (I; R = *p*-MeO·C_6H_4); this amide crystallised from benzene in colourless plates of indefinite m. p. 100—105° (Found : N, 8·95. $C_{26}H_{27}O_6N_3$ requires N, 8·9%). Cyclisation with phosphoryl chloride converted it in a high yield into the *phenanthridine*, which crystallised from alcohol in white microscopic needles, m. p. 190—192° (effervescence) (Found : N, 9·05. $C_{26}H_{25}O_5N_3$ requires N, 9·15%). Its quaternary *methosulphate*, m. p. *ca.* 230°, crystallised from water in deep-yellow needles (Found : N, 7·15; S, 5·45. $C_{28}H_{31}O_9N_3S$ requires N, 7·2; S, 5·45%).

9-*Phenylphenanthridine*-2 : 7-*bistrimethylammonium Iodide* (IV).—2 : 7-Diamino-9-phenylphenanthridine (10 g.) and sodium carbonate (18 g., anhydrous) were refluxed with methanol (100 ml.), water (24 ml.), and methyl iodide (30 ml.) for 8 hours. Two layers at first appeared, but eventually mixed to a deep-purple solution from which crystals slowly separated. The crystals were collected, washed with a little methanol and then with water, and recrystallised from either of these solvents in white needles (14 g.). This salt became yellow at 160°, and with further heating blue-grey, melting at 255° (decomp.) (Found : N, 6·95; I, 40·75. $C_{25}H_{29}N_3I_2$ requires N, 6·7; I, 40·65%).

2 : 7-*Bisdimethylamino-9-phenyl-*10-*methylphenanthridinium Iodide* (V).—The foregoing bisquaternary salt (2·5 g.) was heated in a bath at 180°. Evolution of methyl iodide was observed and after 30 minutes the purple-black mass was extracted with boiling benzene. The residue crystallised from methanol in black needles (1·5 g.) (reddish-purple by transmitted light), m. p. 260—262° (decomp.) (Found : N, 8·8; I, 26·1. $C_{24}H_{26}N_3I$ requires N, 8·7; I, 26·3%). The benzene extract contained a small amount of basic substance, which was not further investigated.

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CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT.
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12.

Catalysed Hydrogen Peroxide Oxidation of Aromatic Hydrocarbons. Part I.

By J. W. COOK and (MISS) R. SCHOENTAL.

A study has been made of the products formed by oxidation of a series of aromatic hydrocarbons (benzene, naphthalene, phenanthrene, anthracene, 1 : 2-benzanthracene, 1 : 2-5 : 6-dibenzanthracene, chrysene, pyrene, and 3 : 4-benzpyrene) with Milas's reagent (hydrogen peroxide in *tert.*-butanol, catalysed by osmium tetroxide). The reagent was diluted with acetone to promote solubility of the polycyclic hydrocarbons, which are sparingly soluble in *tert.*-butanol; the presence of acetone appeared to have no significant influence on the course of the reaction. The products isolated included a *cis*-diol (in the case of phenanthrene and 1 : 2-benzanthracene), quinones, and acids formed by ring-fission.

1 : 2-Benzanthracene and 1 : 2-5 : 6-dibenzanthracene gave not only the 9 : 10-quinones but also the 3 : 4-quinones (XII and XIV) and in spite of the relatively low yields the method furnishes a convenient method of preparation of these *ortho*-quinones. Benzene gave, together with other products, *allo*mucic acid, an interesting example of a simple and direct route from an aromatic hydrocarbon to a sugar acid.

The mechanism of these transformations is discussed, and attention is drawn to their bearing on the mode of biochemical oxidation of the hydrocarbons, for which an exact parallel by purely chemical methods has yet to be found.

THE authors have shown (Cook and Schoental, *J.*, 1948, 170; *Nature*, 1948, **161**, 237) that oxidation of polycyclic aromatic hydrocarbons with Criegee's osmium tetroxide reagent (osmium tetroxide in benzene–pyridine, followed by hydrolysis of the resulting osmic ester) leads to smooth perhydroxylation with formation of homogeneous α-glycols. From the work of Criegee (*Annalen*, 1936, **522**, 75; 1942, **550**, 99) these were clearly *cis*-α-glycols. In nearly every case the positions attacked were different from those at which oxidation is effected by other reagents. The products of osmium tetroxide oxidation were similar in type to some of the compounds which have been isolated from the excreta of animals to which the hydrocarbons were administered (Boyland and Levi, *Biochem. J.*, 1935, **29**, 2679; Boyland and Shoppee, *J.*, 1947, 801; Boyland and Wolf, *Biochem. J.*, 1948, **42**, XXXII; Booth and Boyland, *ibid.*, 1947, **41**, XXIX; 1949, **44**, 361). Such metabolic glycols are probably intermediates in the formation of the phenols which have been isolated in other cases (see, *e.g.*, Weigert and Mottram, *Cancer Res.*, 1946, **6**, 109; Berenblum and Schoental, *ibid.*, p. 699; *Biochem. J.*, 1949, **44**, 604). There are, however, important differences between the osmium tetroxide oxidations and the biochemical oxidations. Usually the positions in the molecules at which oxidation occurs are different in the two cases. Moreover, evidence is accumulating that the metabolic diols which have been isolated are *trans*-α-glycols. The experiments now recorded were initiated in an endeavour to find a reagent which would provide a closer parallel to the biochemical perhydroxylations of aromatic hydrocarbons.

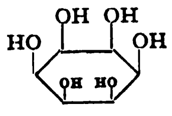
As long ago as 1912, Dakin (" Oxidations and Reductions in the Animal Body," New York) pointed out that hydrogen peroxide, alone of all the known chemical oxidising agents, could bring about the same types of oxidation of a variety of compounds as do enzyme systems, and the widespread occurrence of catalase and peroxidases is a pointer to the importance of hydrogen peroxide in some types of biochemical oxidation. The oxidation of aromatic hydrocarbons by hydrogen peroxide was first reported by Leeds (*Ber.*, 1881, **14**, 975, 1382), who obtained phenol and oxalic acid from benzene, β-naphthol from naphthalene, and anthraquinone from anthracene. In recent years knowledge of the variety of conditions under which oxidations by hydrogen peroxide, and by peroxides and per-acids, can be effected has been widely extended (see, *e.g.*, Waters, *Ann. Reports*, 1945, **42**, 145) and the reaction mechanisms have been extensively studied. It was decided, therefore, to re-examine the oxidation of these hydrocarbons by hydrogen peroxide under varying conditions, and also to examine some more complex polycyclic hydrocarbons which are of interest on account of their carcinogenic activity. The present communication deals mainly with oxidations by hydrogen peroxide in *tert.*-butanol in presence of osmium tetroxide as catalyst. For comparison, some preliminary attention has also been devoted to oxidation by hydrogen peroxide alone, and by hydrogen peroxide catalysed by light, by chloride ions, and by haematin.

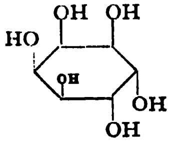
The osmium tetroxide reagent was introduced by Milas and Sussman (*J. Amer. Chem. Soc.*, 1936, **58**, 1302), who showed that olefins are not attacked by a solution of anhydrous hydrogen peroxide in *tert.*-butanol at room temperature until osmium tetroxide is added, whereupon they become oxidised to α-glycols. This reagent was found unsatisfactory in many of the cases which we studied on account of the low solubility of the polycyclic hydrocarbons in *tert.*-butanol. Acetone was therefore used as a solvent in conjunction with the Milas reagent. Treibs (*Ber.*, 1939, **72**, 7) had successfully used acetone as a solvent in catalysed hydrogen peroxide oxidations, but under the conditions which he used he did not apparently observe the formation of the cyclic peroxide of acetone (Wolffenstein, *Ber.*, 1895, **28**, 2265) which we regularly encountered. This appeared to have no significant influence on the course of the reaction. Parallel experiments on the oxidation of benzene by the Milas reagent led to the isolation of the same products, both in presence and in absence of acetone.

RESULTS.

Benzene.—The hydroxylation of benzene by hydrogen peroxide in *tert.*-butanol catalysed by osmium tetroxide has already been reported by Milas and Sussman (*J. Amer. Chem. Soc.*, 1937, **59**, 2345) who obtained phenol in 23% yield. A somewhat higher yield (30%) of phenol was obtained by Milas (*ibid.*, p. 2342) when vanadium pentoxide was used as the catalyst. We also observed the formation of phenol when benzene was treated with the osmium tetroxide catalysed reagent, but if the experiment was continued for several months with excess of hydrogen peroxide a deposit separated, and this was identified as *allo*mucic acid; from the mother-liquors there were isolated also *meso*tartaric and oxalic acids. The transformation of benzene into a sugar acid is noteworthy. It is uncertain whether phenol is an intermediate or whether benzene becomes fully hydroxylated to a hexahydroxy*cyclo*hexane (I or II) which then undergoes ring-fission. This is a point which we are examining. Böeseken and Engelberts (*Proc. Akad. Wetensch. Amsterdam*, 1931, **34**, 1292; 1932, **35**, 750; compare Böeseken and Metz, *Rec. Trav. chim.*, 1935, **54**, 345) have shown that oxidation of phenol by peracetic acid gives, with other products, a 35% yield of *cis-cis*-muconic acid (III). *cis*-Hydroxylation of the double bonds of this acid should give a mixture of *allo*mucic (V) and mannosaccharic (VI) acids [compare Behrend and Heyer, *Annalen*, 1919, **418**, 294, who obtained idosaccharic (VII) and mucic (VIII) acids by oxidation of *trans-trans*-muconic acid (IV) with sodium chlorate in presence of osmium tetroxide]. If a hexahydroxy*cyclo*hexane is formed in our conversion of benzene into *allo*mucic acid then this probably has the completely *cis*-configuration (I). The alternative configuration (II) which could arise from *cis*-addition in pairs of hydroxyl groups to the benzenoid double bonds (see

(I.)





(II.)

January, 1950.

THE CHEMICAL SOCIETY

ANNIVERSARY MEETINGS

Edinburgh—March 29th and 30th, 1950

Wednesday, March 29th.

11 a.m. The Presidential Address, "The Chemical Society—A Mid-Century Review," by Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S. To be delivered in the Chemistry Department, King's Buildings.

12 noon. The 109th ANNUAL GENERAL MEETING.

2 p.m. Coach tours have been arranged as follows:

1. Edinburgh, Cramond Bridge, Forth Bridge. The party will cross on the Ferryboat and return to South Queensferry (tea at The Hawes Inn), Kirkliston, Turnhouse, Edinburgh.
2. Edinburgh, Dalkeith, Lauder, Earlston, Leaderfoot, Sir Walter Scott's View, Bemersyde, Dryburgh Abbey (tea at Dryburgh Abbey Hotel), Mertoun Bridge, St. Boswell's, Leaderfoot, Newstead, Melrose, Abbotsford, Galashiels, Innerleithen, Peebles, Eddleston, Leadburn, Edinburgh.

8.30 p.m. Reception by the University of Edinburgh in the University Library.

Thursday, March 30th.

10 a.m. Annual Meeting of Local Representatives—King's Buildings Common Room.

11.30 a.m. Faraday Lecture, "The Application of Radioactive Indicators in Biochemical Studies," by Professor G. Hevesy, For.Mem.R.S., Honorary Fellow. To be held in the Zoology Department, King's Buildings. The Lecture will be followed by the presentation of the Faraday Medal to the Lecturer.

7 p.m. for 7.30. Anniversary Dinner at which the new President of the Society will be formally installed. To be held at the North British Station Hotel.

Further particulars and forms of application for tickets are being sent to Fellows.

The Royal Institute of Chemistry

Fellows of the Society attending the Anniversary Meetings of the Royal Institute of Chemistry on March 31st and April 1st can reach Glasgow by the following trains.

Depart	Edinburgh (Waverley)	8.10 a.m.	9.5 a.m.
Arrive	Glasgow	9.20 a.m.	10.8 a.m.

SCIENTIFIC MEETINGS DURING MARCH AND APRIL, 1950

LONDON.

Thursday, March 2nd, 1950, *at* 7.15 *p.m.*

Centenary Lecture, **The Azulenes,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the Main Chemistry Lecture Theatre, The Imperial College of Science and Technology, S.W.7.

Thursday, March 16th, 1950, *at* 7.15 *p.m.*

The following papers will be read and discussed:

"The significance of the bromine cation in aromatic substitution. Parts I and II." By D. H. Derbyshire and W. A. Waters.

"The kinetics of aromatic halogen substitution. Part VII. Nitrobenzene and azobenzene." By P. W. Robertson, T. R. Hitchings, and G. M. Will.

"The effect of bond structure on the transformation of *o*-aroyloxyacetoarones into *o*-hydroxydiaroylmethanes—Baker–Venkataraman transformation." By N. V. Nowlan, P. A. Slavin, and T. S. Wheeler.

To be held at Burlington House, W.1.
Abstracts of the papers may be obtained from the General Secretary.

ABERDEEN.

Thursday, March 9th, 1950, *at* 7.30 *p.m.*

Lecture, **The Chemistry of Anæsthetics,** by Professor H. B. Nisbet, D.Sc., F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Chemistry Department, Marischal College, Aberdeen.

BIRMINGHAM.

Friday, March 17th, 1950, *at* 4.30 *p.m.*

Lecture, **How Crystals Grow,** by Professor E. K. Rideal, M.B.E., M.A., D.Sc., F.R.S.

To be held in the Main Chemical Lecture Theatre, Chemistry Department, The University, Edgbaston, Birmingham.

EDINBURGH.

Thursday, March 16th, 1950, *at* 7.30 *p.m.*

Lecture, **Some Aspects of Photo-oxidation with Reference to Chlorophyll,** by Dr. M. Ritchie.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the North British Station Hotel, Edinburgh.

EIRE.

Wednesday, March 1st, 1950, *at* 7.45 *p.m.*

Lecture, **Deoxy-sugars and Nucleic Acids,** by Professor M. Stacey, D.Sc., F.R.I.C.

Joint meeting with the Irish Chemical Association, the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Department of Chemistry, University College, Dublin.

Friday, March 3rd, 1950, *at* 7.45 *p.m.*

Lecture, **Bacterial Nucleic Acids,** by Professor M. Stacey, D.Sc., F.R.I.C.

Joint meeting with the Irish Chemical Association, the Royal Institute of Chemistry, and the Society of Chemical Industry, to be held at University College, Cork.

Monday, March 6th, 1950, *at* 7.45 *p.m.*

Lecture, **Deoxy-sugars and Nucleic Acids,** by Professor M. Stacey, D.Sc., F.R.I.C.

Joint meeting with the Irish Chemical Association, the Royal Institute of Chemistry, and the Society of Chemical Industry, to be held in the Chemical Laboratories, University College, Galway.

Wednesday, March 8th, 1950, *at* 7.45 *p.m.*

Lecture, **Lycomarasmin : The Chemistry of Wilting Diseases,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the Department of Chemistry, Trinity College, Dublin.

GLASGOW.

Friday, March 10th, 1950, *at* 7.15 *p.m.*

Lecture, **Purine Synthesis—A New Chapter,** by Dr. A. H. Cook, F.R.I.C.

Joint meeting with local Chemical Societies, to be held in the Chemistry Department, The University, Glasgow.

HULL.

Thursday, March 2nd, 1950, *at* 6 *p.m.*

Lecture, **Aromatic Nitration,** by Dr. G. M. Bennett, C.B., M.A., F.R.S.

Joint meeting with the Royal Institute of Chemistry, to be held at University College, Hull.

LIVERPOOL.

Tuesday, March 7th, 1950, *at* 4.30 *p.m.*

Lecture, **Lycomarasmin : The Chemistry of Wilting Diseases,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the Chemistry Department, The University, Liverpool.

Thursday, March 16th, 1950, *at* 4.30 *p.m.*

Lecture, **Heterogeneous Catalysis,** by Professor E. K. Rideal, M.B.E., M.A., D.Sc., F.R.S.

To be given in the Chemistry Lecture Theatre, The University, Liverpool.

Thursday, March 23rd, 1950, *at* 4.30 *p.m.*

Lecture, **Photo-excited Electron-transfer Reactions,** by Professor M. G. Evans, D.Sc., F.R.S.

To be given in the Chemistry Lecture Theatre, The University, Liverpool.

(*Note :* Professor Evans' Lecture has been postponed from March 16th to 23rd.)

MANCHESTER.

Friday, March 3rd, 1950, *at* 6.30 *p.m.*

Centenary Lecture, **The Azulenes,** by Professor Dr. Pl. A. Plattner (Zürich).

To be given in the University, Manchester.

Thursday, March 9th, 1950, *at* 6.30 *p.m.*

Pedler Lecture, **Polycyclic Aromatic Hydrocarbons,** by Professor J. W. Cook, D.Sc., Ph.D., F.R.S.

To be given in the Chemistry Department, The University, Manchester.

Wednesday, March 22nd, 1950, *at* 6.30 *p.m.*

Lecture, **Some Recent Applications of Infra-red Spectroscopy,** by Dr. H. W. Thompson, M.A., F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held at the Engineer's Club, Manchester.

NORTHERN IRELAND.

Friday, March 10th, 1950, *at* 7.30 *p.m.*

Lecture, **Inorganic Chromatography,** by Mr. R. A. Wells, B.Sc., A.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Agricultural Lecture Theatre, Elmwood Avenue, Belfast.

NOTTINGHAM.

Thursday, March 9th, 1950, *at* 6.30 *p.m.*

Lecture, **Some Aspects of Structural Chemistry,** by Professor W. Wardlaw, C.B.E., D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society, to be held in the Lecture Theatre, Department of Chemistry, The University, Nottingham.

ST. ANDREWS and DUNDEE.

Thursday, April 13th, 1950, *at* 5 *p.m.*

Lecture, **Chemical Reactions induced by Nuclear Radiations,** by Dr. F. S. Dainton, M.A.

To be given in the Chemistry Department, University College, Dundee.

SHEFFIELD.

Thursday, March 16th, 1950, *at* 5.30 *p.m.*

Lecture, **Recent Developments in Acetylene Chemistry,** by Professor E. R. H. Jones, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society, to be held in the Chemistry Lecture Theatre, The University, Sheffield.

Thursday, April 27th, 1950, *at* 5.30 *p.m.*

Lecture, **Recent Advances in the Chemistry of the Steroids,** by Professor F. S. Spring, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Sheffield.

SOUTHAMPTON

Friday, March 3rd, 1950, *at* 5 *p.m.*

Lecture, **The Determination of Traces of Elements and Compounds,** by Dr. H. Irving, M.A., F.R.I.C.

Joint meeting with University College Chemical Society, to be held in the Physics Department, University College, Southampton.

Wednesday, April 26th, 1950, *at 7 p.m.*

Lecture, **Trace Elements in Plant Life,** by Dr. W. A. Roach, A.R.C.S., A.R.I.C.

Joint meeting with Mid-Southern Counties Section of the Royal Institute of Chemistry and Portsmouth and District Chemical Society, to be held at the Municipal College, Portsmouth.

SOUTH WALES.

Friday, March 3rd, 1950, *at 5.30 p.m.*

Lecture, **Synthetical Investigations in the Series of Cyclic Imines,** by Professor F. E. King, M.A., D.Phil.

Joint meeting with University College of Swansea Students' Chemical Society, to be held in University College, Swansea.

PROCEEDINGS
OF THE
CHEMICAL SOCIETY

Minutes of a
SCIENTIFIC MEETING
held at Burlington House on Thursday, December 15th, 1949, at 7.15 p.m.

Dr. J. KENYON, F.R.S., Vice-President, was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at the Royal Institution on Wednesday, November 30th, 1949, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: S. K. Hutchinson, E. M. Joiner, A. R. Katritzky, D. J. R. Laurence, A. C. Heathfield, J. Madinaveitia.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

" Some Physico-chemical Properties of Acridine Antimalarials with Reference to their Biological Action." By D. Ll. Hammick and S. F. Mason.

" The Properties of Freshly Formed Surfaces. Parts XI–XIV." By C. C. Addison and S. K. Hutchinson.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
John Evelyn Cave-Brown-Cave (Ilford)	Feb. 7th, 1946.	Nov. 10th, 1949.
Arthur Jenner Chapman (Chalfont St. Giles)...	Dec. 5th, 1895.	Nov. 9th, 1949.
Benedict Trembath Kitto (Gerrard's Cross) ...	Dec. 6th, 1917.	Sept. 1949.

CONGRATULATIONS.

The President has conveyed the congratulations of the Council to the following Fellows whose names appear in the New Year Honours List:

Knight Bachelor

Sidney John Saint

C.B.

Owen Haddon Wansbrough-Jones

C.B.E.

Frederick Hardy
Frederick George Soper

ELECTION OF NEW FELLOWS.

The following 36 candidates were elected Fellows of the Society on December 15th, 1949:

Arthur Billing Angus.
Morrell Kenneth Aston.
John Dennis Butler.
Josephine Natalie Cartwright.
Denis Michael Comber.
Alexander Latimer Davidson.
Austen Emlyn Davies.
Michael Trevor Davies.
John Owen Dawson.
John Albert Durant.
Dennis Brian Freeman.
Robert Arthur Hall.
Elbert Everett Harris.
Robert Johnston.
David Thomas King.
Mark Long.
Minoo Dossabhoy Mehta.
David Fisher Muggleton.
Derek Payne.
Donald George Peacock.
Peter William Sadler.
Allen W. Scholl.
Raymond B. Seymour.
Kenneth Shorrock.
Shivagangay Siddappa.
Bratislav G. Simek.
Brian Willliam Stannard.
John Ernest Stone.
Stig Arne Sunner.
Harry Callender Sutton.
Frederick Maurice Tayler.
Alexander Patrick Tulloch.
William Hughes Wadman.
Charles Wickham-Jones.
Alfred Peter Wolf.
Richard William Young.

MEETING OF COUNCIL.

A meeting of Council was held on December 15th, 1949.

The report of the meeting of the Publication Committee held on November 17th, 1949, was received, and approval was given to a recommendation that, in papers submitted for publication in the Journal, the names of new compounds should henceforth be italicised only in the Experimental section (at their first mention excluding headings). The use of italics in the Introduction and in the Summary will be abandoned.

The thanks of the Council have been conveyed to the Pharmaceutical and Allied Chemicals Disposals Association, Ltd., for a donation towards the cost of publications and to Dr. R. Raper for a gift of the Society's publications.

The reports of the meetings of the Joint Library Committee and the Research Fund Committee held on November 23rd, 1949, were received.

Certain matters of a formal and financial nature were conducted.

CORDAY-MORGAN MEDAL.

The award of the Corday–Morgan Medal in respect of the year 1949 will receive consideration by Council early in 1951. Applications submitted by, or on behalf of, candidates must be received at the Society's apartments in Burlington House, not later than December 31st, 1950. The award consists of a Silver Medal designed by Mr. Percy Metcalfe, C.V.O., and a cash prize amounting to not less than £150.

The following rules govern the award:

1. The Award shall be known as the Corday–Morgan Medal.

2. The Award shall be made annually to the chemist of either sex and of British nationality who, in the judgment of the Council of the Chemical Society, shall have published during the year in question the most meritorious contribution to experimental Chemistry, and who, at the date of publication, shall not have attained the age of thirty-six years. The date of publication of any journal shall be deemed to be the date at which the journal was first available to the public.

3. The Award shall not be made more than once to the same candidate.

4. The Council may at its discretion suspend the Award in any year in which no suitable candidate presents himself or is brought to the notice of the Council. In the event of such suspension a sum equal to the income otherwise available for the Award in that year shall be invested and added to the capital of the Trust Fund.

5. The Award shall consist of a silver medal and a monetary prize amounting to the balance of the income of the Trust Fund for the year, after payment of the expenses incidental to the Award.

6. No restrictions shall be placed upon the branch of chemistry for which the Award is granted, or upon the place in which the work is conducted.

7. The merits of the work of any candidate for the Award may be brought to the notice of the Council either by persons who desire to recommend the candidate or by the candidate himself.

8. Details of the Award shall be published annually in the *Proceedings of the Chemical Society* and elsewhere.

9. Applications, or recommendations for the Award, accompanied by offprints or copies of any published work on which the grant of the Award is to be judged, shall be forwarded so that they shall reach the Society not later than the thirty-first day of December in the year following that for which the Award is to be made.

10. Each candidate shall give the names of two persons with a knowledge of his work, to whom references can be made by the Society.

11. The Award shall be presented at a meeting of the Society.

12. If any doubt shall arise as to the correct interpretation of these rules, the matter shall be decided by the Council of the Chemical Society.

13. The Council may from time to time alter or add to the regulations for the administration of the Award, provided that no regulation shall be approved that is contrary to the terms of the Bequest as expressed in the will of the late Sir Gilbert T. Morgan.

LIBRARY REGULATIONS.

The regulations governing the use of the Library of the Chemical Society have been amended by the Joint Library Committee and approved by the Chemical Council. The following are the revised rules :

1. The Library is open from 10 a.m. to 9 p.m. daily, except on Saturdays and from the 16th July to the 30th September, inclusive, when it closes at 5 p.m. The Library is closed on Christmas Eve, Bank Holidays and the day after, and at 1 o'clock on the day preceding Good Friday and Christmas Eve. The times may be varied from time to time, as the Joint Library Committee may determine.

2. Every person on first entering the Library on any day must sign a book provided for the purpose.

3. Silence must be maintained in the Reading Room and smoking is not permitted.

4. No marks of any kind may be made in the Library books or periodicals, and no papers or books may be placed on them.

5. Borrowers are not allowed to have on loan more than six volumes at a time, without special permission from the Librarian.

6. Dictionaries, Pamphlets of which there are not duplicate copies, and certain early chemical and other books belong to the Reference Library, and are not for general circulation. Persons desiring to borrow books from the Reference Library must make special application to the Librarian, who may then, at his discretion, issue such volumes for a period not exceeding one month.

7. Journals of which the Society does not possess duplicate copies may not be borrowed, except for one night, or from Saturday to Monday. The privilege does not extend to volumes of special value or rarity, and will not be continued to any person who does not strictly comply with these conditions.

8. A new book may not be borrowed or bespoken until one month after it has been added to the Library.

9. No reader may remove a book from the Library without filling up and handing to a member of the Library staff one of the loan receipt slips provided for the purpose. This slip will be returned to the borrower on the return of the book.

10. Books are issued to the person desiring the loan, or to anyone bringing a signed order from such person. In either case a receipt must be given on the form provided. When a person desires a book or books to be forwarded, a signed request must be sent to the Librarian and the whole cost of the carriage paid. The Librarian may also issue books in response to a telephoned request from a person entitled to borrow, subject to the con-

ditions that the request is subsequently confirmed in writing, and that the parcel be posted to an address registered with the Librarian. All books borrowed shall be at the risk of the borrower from the moment they are issued or dispatched by the Librarian, and until they are returned to the Librarian. Volumes returned through the post must be securely packed in a box, or otherwise protected to prevent injury.

11. The privilege of borrowing is a personal one, and borrowers are therefore not permitted to re-lend volumes or to borrow them for consultation by others.

12. Books may not be sent or taken out of the British Isles.

13. Borrowers shall be at liberty to retain a book one calendar month, unless, at the expiration of a fortnight, notice is received that the book is required by another person, in which case it must be returned at once. Single parts of journals may not be retained longer than one week. No volume may be re-issued to the same borrower until at least seven days have elapsed after its return, neither may it be transferred by one borrower to another.

14. Borrowers retaining books longer than the time specified, and neglecting to return them when demanded, shall forfeit the right to borrow books from the Library until the volume or volumes be returned, and for such further time as the Joint Library Committee may determine.

15. Persons to whom books have been issued shall be held responsible for their preservation from injury; and if any book when returned is found to have been damaged, the Council of the Chemical Society may order that it be repaired or replaced at the expense of the borrower. In the event of any book being lost or being detained after application has been made for its return, the Council of the Chemical Society may replace, at the cost of the borrower, the volume or volumes so lost or detained, or, if the book cannot be replaced, may require suitable compensation from the borrower. This regulation shall also apply to single parts of periodicals.

16. For the purpose of revision and cleaning, the Library shall be closed for a fortnight in each year, before which time all books must be returned, unless special permission has been previously obtained from the Librarian. In the event of any book not being returned on such occasion, the Council of the Chemical Society may replace it at the cost of the borrower.

17. Persons who are neither members of the Constituent Bodies nor members of contributing Societies, may be permitted to use the Library for reference purposes for a period not exceeding one week, upon the written introduction of a member of a Constituent Body, or upon the production of satisfactory references or recommendations to the Librarian.

18. Violation of any regulation renders the person concerned liable to suspension of Library privileges for such time as the Chemical Council may direct.

RESEARCH GRANTS.

The Council have approved the following grants from the Research Fund:

	£	s.	d.
Cambridge, Laboratory of Physical Chemistry			
Mr. P. Smith. "Polymerisation of acrylonitrile photosensitised by hydrogen peroxide in aqueous solution"	30	0	0
Huddersfield, Technical College			
Dr. G. R. Ramage. "β-Caryophyllene"	20	0	0
Leeds, The University			
Dr. N. H. Hartshorne. "Kinetics of polymorphic change"	25	0	0
Leicester, University College			
Dr. C. Eaborn. "Reactions of organo-silicon compounds"	15	0	0

	£	s.	d.
London, Birkbeck College			
Mr. V. M. Ingram. " Autolysis products of pepsin "	20	0	0
London, Chelsea Polytechnic			
Dr. A. M. James. " Some investigations of the colloidal behaviour of micro-organisms "	70	0	0
London, Imperial College			
Dr. D. H. R. Barton. " Application of the method of molecular rotation differences to steroids "	20	0	0
Mr. P. J. Dyne. " Study of ionisation potentials and critical potentials of polyatomic molecules "	30	0	0
London, King's College			
Mr. E. G. Ansell. " Sugar Nitrates "	10	0	0
Dr. J. Honeyman. " Synthesis of fructofuranose derivatives "	20	0	0
Mr. E. G. Jefferson. " Kinetics of acylation reactions "	15	0	0
Mr. J. A. Saunders. " Molecular compounds "	13	0	0
Mr. D. Thompson. " Synthesis of pyrethrin analogues for a study of the relationship between constitution and insecticidal action "	20	0	0
Mr. R. A. Thompson. " Synthesis of chrysanthemum mono- and di-carboxylic acids and related acids for use in the synthesis of pyrethrin analogues "	10	0	0
London, Royal Holloway College			
Mrs. K. Mackay. " Additional and polymerisation reactions "	10	0	0
London, Queen Mary College			
Mr. M. F. Ansell. " Intra molecular acylation of α- and β-substituted β-1-naphthylpropionic acids "	20	0	0
Mr. D. F. Muggleton. " Electrical conductivity of salts in some non-aqueous solvents having large molecules "	20	0	0
Newcastle-on-Tyne, University College			
Dr. J. Weiss. " Investigations on free radicals in solution "	30	0	0
New Zealand, Auckland University College			
Dr. L. H. Briggs. " Plant products of New Zealand "	50	0	0
Oxford, Dyson Perrins Laboratory			
Mr. M. C. Ford. " An investigation of heterocyclic free radicals "	17	15	0
Oxford, Inorganic Chemistry Laboratory			
Mr. L. A. K. Staveley. " Low-temperature calorimetry "	20	0	0
Southampton, University College			
Dr. A. R. Burkin. " Compounds of long-chain aliphatic amines with metal salts. Reversible dissociation of acid-radicals from complex molecules in non-aqueous solutions "	20	0	0
Dr. Ishbel G. M. Campbell. " Configuration of heterocyclic antimony compounds "	15	15	0
Dr. N. B. Chapman. (*a*)" Kinetics of replacement of halogen atoms in benzenoid and heterocyclic systems." (*b*) " Synthesis of potential histamine antagonists "	30	0	0

Swansea, University College

	£	s.	d.
Mr. R. J. Bridgwater. " Stereochemistry and replacement reactions of the coprostanyl chlorides "	10	0	0
Mr. G. Roberts. " Stereochemistry and replacement reactions of cholesteryl chloride and the cholestanyl chlorides "	10	0	0

CIPHERING SYSTEMS FOR ORGANIC STRUCTURAL FORMULÆ.

The International Union of Pure and Applied Chemistry has appointed a Commission to examine and develop a ciphering system for organic structural formulæ. In receiving the report of this Commission, the British National Committee for Chemistry decided to call the attention of British chemists to the following wish expressed by the Commission : " In order to facilitate full consideration by the Commission before the next Conference of the Union in Washington in 1951, ciphering systems should be submitted before March 1st, 1950, to the Commission's Acting Secretary, Professor J. W. Perry, Room 20–E–215, Massachusetts Institute of Technology, Cambridge 39, Mass., U.S.A. Persons submitting ciphering systems will be asked to demonstrate their effectiveness by applying them to certain tests set up by the Commission."

INTERNATIONAL UNION OF CRYSTALLOGRAPHY.

The Executive Committee of the International Union of Crystallography has accepted a kind invitation from the Swedish National Committee of Crystallography to hold the Second General Assembly and International Congress in Stockholm from June 27th to July 3rd, 1951. These dates have been chosen in consultation with the Swedish National Committee and with the National Committee of each of the Adhering Bodies. It is hoped that this early notice will make it possible for crystallographers throughout the world to arrange to attend.

Further particulars of the meeting will be given from time to time.

INTERNATIONAL CONGRESS ON ANALYTICAL CHEMISTRY—1952.

Plans are now being prepared for an International Congress on Analytical Chemistry to be held in Britain in 1952 under the patronage of the International Union of Chemistry. The Executive Committee, which has had preliminary discussions with regard to the location of the Congress, publication of papers, and other matters, is under the Chairmanship of Mr. G. Taylor, F.R.I.C. The Chairman of the General Committee is Sir Robert Robinson, O.M., P.R.S., and the Honorary Secretary of the Congress is Mr. R. C. Chirnside, F.R.I.C., Research Laboratories of the General Electric Co., Ltd., Wembley.

A further announcement will be made in due course.

AMERICAN CHEMICAL SOCIETY—MEETING ON RUBBER CHEMISTRY.

The Division of Rubber Chemistry of the American Chemical Society is holding an International Meeting in Cleveland, Ohio, U.S.A., on October 11th, 12th, and 13th, 1950. This meeting is open to all scientists and technologists active in the field of rubber.

Papers are invited from members of scientific societies from all countries. Such papers should pertain to the structure of rubber, mechanism of vulcanisation, ageing, etc., polymerisation of synthetic rubbers, study of rubber latex and its applications, and other phases of rubber technology including processing and manufacturing procedures.

Those wishing to submit papers should contact Mr. C. R. Haynes, Secretary of the Division of Rubber Chemistry, Binney and Smith Co., 41 East 42nd Street, New York 17, New York, forwarding an abstract of approximately 400 words describing their papers. All papers must be presented in English. Such abstracts should reach Mr. Haynes before July 1st, 1950.

MEETINGS OUTSIDE LONDON

EIRE.

"The Head-to-tail Isoprene Rule and its Bearing on Terpene Chemistry," by Professor G. R. Clemo, D.Sc., F.R.S.

A joint meeting with the Werner Society was held in the Chemistry Lecture Theatre, Trinity College, Dublin, on November 25th, 1949, with Professor W. Cocker in the Chair.

The lecture was followed by an interesting discussion, and the chairman conveyed the thanks of the meeting to Professor Clemo.

NOTTINGHAM.

Meeting for the reading of original papers.

A joint meeting with the University Chemical Society was held in the Department of Chemistry of the University on December 1st, 1949, with Professor F. E. King in the Chair.

The following papers were read:

"Antituberculous compounds. Part V. 2-Sulphanimilamido-5-alkyl-1 : 3 : 4-oxa- and -thia-diazoles and related *iso*thiosemicarbazones and *iso*thioureas," by J. D. Brooks, P. T. Charlton, P. E. Macey, D. A. Peak, and W. F. Short.

"The crystal structure of a complex between quinol and methyl cyanide," by H. M. Powell and S. C. Wallwork.

Dr. M. W. Partridge, on behalf of those present, warmly thanked Dr. Peak and Mr. Wallwork, who read the papers.

LIST OF APPLICATIONS FOR FELLOWSHIP

(*Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the* Journal *for January,* 1950. *Such objections will be treated as confidential. The forms of application are available in the Library.*)

***Addison, William Eric,** B.Sc. (Glas.). British. Chemistry Department, Marischal College, Aberdeen. Assistant Lecturer. *Signed by :* R. M. Barrer, J. M. C. Thompson, R. B. Strathdee.

***Alford, Ernest James,** B.Sc. (Lond.). British. Exton Farm, Exton, near Exeter. Research Student at University College of the South West. *Signed by :* S. J. Gregg, K. Schofield, H. T. S. Britton.

Anderson, Alan James, B.Sc. (Lond.). British. 194, Cambridge Road, Seven Kings. Student. *Signed by :* D. S. Hoare, K. R. Rees, K. M. Jackson.

Anderson, William, B.Sc. (Lond.), A.R.I.C. British. 24, Camphill Avenue, Langside, Glasgow, S.1. *Signed by :* H. C. Moir, J. J. Doyle, A. G. Bishop.

***Asher, Raymond Cecil.** British. Lynton, Highbury Road, Anna Valley, near Andover. Student at University College, Southampton. *Signed by :* K. R. Webb, E. Cartmell, J. D. Sutton.

***Babbs, John Walter,** B.Sc. (Lond.). British. 45, Costons Avenue, Greenford. Chemist at Research Association of British Rubber Manufacturers, Croydon. *Signed by :* J. R. Partington, H. H. Neville, N. Lindop.

***Bailey, John Martyn,** B.Sc. (Wales). British. The Limes, Hawarden, Chester. Research Student. *Signed by :* S. Peat, W. R. Angus, W. J. Whelan.

Banfield, Thomas Arthur, Ph.D. (Lond.), A.R.C.S., D.I.C., F.R.I.C. British. British Paints Ltd., Marine Division, Creekmouth, Barking. Research Chemist. *Signed by :* F. Wormwell, D. M. Brasher, W. H. J. Vernon.

Barbour, William Arthur Shute, B.Sc. (Glas.). British. No. 11452, c/o A.I.O.C., S.Q.852/2, Abadan, S. Iran. Chemist at Anglo-Iranian Oil Co. Ltd. *Signed by :* M. H. Silk, J. N. Watson, D. Emsley.

***Barnes, John Herbert,** M.Sc. (Manc.). British. 10, Robin Hood Way, Greenford. Research Chemist at Glaxo Laboratories Ltd. *Signed by :* B. A. Hems, J. C. Clayton, J. Elks.

Beech, Frederick Walter, B.Sc. (Birm.), A.R.I.C. British. Department of Horticulture and Agriculture, Research Station, Long Ashton, Bristol. Cider Chemist. *Signed by :* L. F. Burroughs, M. E. Kieser, H. Martin.

***Bharucha, Kekhusroo Rustomji,** M.Sc. (Bombay). Indian. 42, Stanhope Gardens, Highgate, N.6. Research Student at Imperial College. *Signed by :* B. C. L. Weedon, R. P. Linstead, J. A. Elvidge.

***Bookey, John Bernard,** B.Sc. (Lond.), A.R.C.S. British. 1, Cranhurst Road, N.W.2. Research Chemist. *Signed by :* H. V. A. Briscoe, C. Goodeve, A. A. Eldridge.

Bottomley, Robert Alwyn, M.Sc. (Melbourne), Ph.D. (Minnesota). British. c/o Golden Crust Bakery Ltd., Gover Street, North Adelaide, South Australia. Director of Research. *Signed by :* R. D. Mason, G. H. Edwards, L. S. Bull.

Bradford, Leslie, B.Sc. (Birm.), A.R.I.C. British. 69, Brentford Road, Kings Heath, Birmingham, 14. Research Student at Birmingham University. *Signed by :* S. R. Carter, M. Stacey, L. F. Wiggins.

Braybrooks, William Ewart, Ph.D. (Leeds). British. c/o British Leather Manufacturers' Research Association, 1—6, Nelson Square, S.E.1. Research Chemist. *Signed by :* R. N. Johnson, R. F. Innes, H. Phillips.

Broadbridge, Donald Frederick, A.R.I.C. British. 2, Elm Road, Bedfont. Industrial Chemist. *Signed by* : N. A. C. Pryce, D. A. Tame, B. P. Baker.

Bunnett, Joseph Frederick, B.A. (Reed College), Ph.D. (Rochester). American. Chemistry Department, University College, Gower Street, W.C.1. Fulbright Research Scholar. *Signed by :* D. P. Craig, R. S. Nyholm, G. Kohnstam.

Caldwell, Dennis, B.Sc. (Lond.), A.R.I.C. British. 30, West Street, Hertford. Development Chemist. *Signed by :* J. H. Hunt, M. R. Campbell, M. E. H. Fitzgerald.

***Cast, John.** British. 84, Sycamore Road, Nottingham. Student. *Signed by :* A. H. Lamberton, J. Barratt, D. H. Peacock.

***Cummins, Ernest George.** British. 126, Wadham Gardens, Greenford. Assistant Research Chemist. *Signed by :* J. E. Page, E. L. Smith, J. G. Waller.

***Daly, James Joseph.** British. 341, Cupar Street, Belfast. Student. *Signed by :* H. Graham, C. L. Wilson, E. M. Reid.

Davies, Lewis Maldwyn, B.Sc. (Wales), A.R.I.C. British. 7, St. Patricks Road, Coventry. Research Chemist. *Signed by :* R. H. Davies, E. E. Ayling, J. E. Coates.

Davis, John Edward, F.R.I.C. British. South Eastern Gas Board, Katharine Street, Croydon. Chief Technical Officer. *Signed by :* H. Stanier, J. R. Dewhurst, E. A. Bucknell.

***Davis, Stanley Joseph.** British. 80, Ferndene Road, Denmark Hill, S.E.24. Research Student. *Signed by :* A. I. Vogel, G. H. Jeffery, L. Ellison.

Dent, Peter Alan. British. The Farmhouse, Great Salterns, Portsmouth. Student. *Signed by :* K. C. Aylett, J. M. Wilson, C. G. Lyons.

***Dick, Leslie Creighton.** British. 113, Heaton Terrace, Billy Mill, North Shields. Research Student. *Signed by :* P. H. Plesch, G. N. Burkhardt, G. F. Woods.

Doyle, Frank Peter, M.Sc. (Lond.), A.R.I.C. British. 37, Nutfield Gardens, Goodmayes, Ilford. Research Chemist. *Signed by :* E. de Barry Barnett, J. D. Kendall, R. B. Collins.

Drakeley, Kenneth Douglas, A.R.I.C. British. 39, Woodstock Road, Moseley, Birmingham, 13. Industrial Chemist. *Signed by :* E. G. K. Pritchett, G. Barnett, C. E. Scoffom.

Evans, John Gwynant, M.Sc.Tech. (Manc.). British. Bradford Dyers Association Ltd., 39, Well Street, Bradford. Chief Chemist. *Signed by :* E. H. Rodd, J. R. Maddocks, W. J. S. Naunton.

***Faulkner, Gordon James.** British. 54, Ashton Road, Bristol, 3. Laboratory Assistant. *Signed by :* M. W. Vincent, D. Powell, G. F. Oliver.

Ford, Leslie Harry, Ph.D. (Birm.), A.R.I.C. British. 5, Culmington Road, Ealing, W.13. Chief Chemist, Williams (Hounslow) Ltd. *Signed by :* M. Stacey, C. H. R. Elston, J. P. Philpot.

Friedmann, Charles Aubrey, D.Phil. (Oxon.), M.Sc. (Witwatersrand). British. 2, Cadogan Square, Sloane Square, S.W.1. Research Chemist. *Signed by :* J. W. H. Oldham, H. M. E. Cardwell, C. C. Culvenor.

Garden, William David, B.Sc. (Glas.). British. 38, Thornwood Drive, Glasgow, W.1. Student. *Signed by :* F. D. Gunstone, C. Buchanan, J. D. Loudon.

***Gibbs, Brian Montague,** B.Sc. (Lond.), A.R.I.C. British. Research/B Department, Lever Bros., Port Sunlight, Ltd., Port Sunlight, Cheshire. Chemist. *Signed by :* W. K. Smith, B. C. Christian, A. D. Scott.

***Goddard, Harry.** British. 16, Melville Avenue, Balby, Doncaster. Works Chemist. *Signed by :* F. Broomhead H. Wilson, S. Critchley.

Hall, Michael Geoffrey, B.Sc. (Lond.), A.R.I.C. British. 17, Snowdon House, Highways Hostel, Euxton, near Chorley. Scientific Officer, M.O.S. (Chemical Inspectorate). *Signed by :* J. R. Sanderson, T. P. Gervis, F. J. Woodman.

***Harrison, Douglas.** British. 63, Grantham Road, Radcliffe-on-Trent, Nottingham. Student at Queen Mary College. *Signed by :* C. M. French, R. F. Garwood, N. Lindop.

Harte, Margaret, B.Sc. (N.U.I.). Irish. Monsanto Chemicals, Ltd., Ruabon, Wrexham, Denbighshire. Librarian. *Signed by :* J. W. Barrett, W. D. Scott, M. N. Strachan.

***Haslam, Alwyn Aubrey.** British. 3, Dorothy Road, Hazel Grove, Stockport. Student at Manchester University. *Signed by :* C. Campbell, M. C. Whiting, H. B. Henbest, T. H. H. Quibell.

***Hayes, Donal Herbert,** B.A. and B.Sc. (T.C.D.). British. Windgate House, Greystones, Co. Wicklow. Research Student. *Signed by :* C. Lipman, W. Cocker, K. C. Bailey.

Heilpern, Edith Erna, M.Chem. (Cracow). British. 160, Ridge Road, Sutton. Scientific Information Officer. *Signed by :* A. Elce, C. B. Maddocks, D. P. Young.

Hermann, Fritz Jacob, D.Sc. (Utrecht). Dutch. 34, rue Parmentier, Neuilly (Seine), France. Technical Director, Société Française Beckacite, Resine Synthetiques. *Signed by :* H. W. Keenan, G. Swann, H. R. Touchin.

***Horn, James Arnot,** B.Sc. (Glas.), A.R.I.C. British. 77, Stevenston Road, Kilwinning. Research Student at Royal Technical College, Glasgow. *Signed by :* G. Edwards, W. Gibb, F. Rumford.

***Housley, Eric,** B.Sc. (Lond.). British. 35, Swaddale Avenue, Japton, Chesterfield. Plant Control Chemist. *Signed by :* J. Gumb, H. F. Bondy, R. P. Marshall.

Howes, Donald Albert, D.Sc. and Ph.D. (Birm.), F.R.I.C. British. 54, Magnolia Avenue, Larchmont, New York, U.S.A. *Signed by :* H. M. Stanley, S. F. Birch, F. Roffey.

Ho-Yen, Joseph Ephraim, B.Sc. (Lond.), A.R.I.C. British. 10A, Campden Hill Gardens, W.8. Assistant Analyst. *Signed by :* T. McLachlin, F. A. Lyne, J. M. Jones.

Ismay, Doreen, B.Sc. (Lond.). British. The Frythe, Welwyn. Chemist, Butterwick Research Laboratories. *Signed by :* J. F. Grove, J. Chatt, T. P. C. Mulholland.

Johnson, Frank Pace, B.Sc. (Lond.), A.R.I.C. British. 81, Barrows Green Lane, Widnes. Research Chemist. *Signed by :* L. A. Haddock, A. G. Jones, H. K. Southern.

Johnson, John Terrence George, F.R.I.C. British. 10, Allenby Road, Forest Hill, S.E.23. Chemist, Whitbread & Co., Ltd. *Signed by :* B. M. Brown, E. B. Wright, H. F. P. Webber.

***Jones, David Morris,** B.Sc. (Wales). British. Bronallt, Barmouth, Merioneth. Student. *Signed by :* S. Peat, W. R. Angus, W. J. Whelan.

***King, Norman Percival.** British. 300, Upper Weston Lane, Woolston, Southampton. Student. *Signed by :* K. R. Webb, N. B. Chapman, A. R. Burkin.

Lee, Henry Ramsden, B.Sc. (Sheffield), A.R.I.C. 8, Rydal Road, Ulverston, Lancs. Production Chemist. *Signed by :* E. F. D. Winter, F. W. Anderson, G. L. Hollis.

***Lewis, Donald George,** B.Sc. and Ph.D. (Lond.), D.I.C. British. Chemistry Department, University College, Swansea. Lecturer. *Signed by :* R. J. Bridgwater, E. E. Ayling, R. H. Davies.

***Lewis, Reginald Norman,** B.A. (Cantab.), A.R.I.C. British. 52, Allman Road, Erdington, Birmingham, 24. Research Chemist. *Signed by :* A. McM. Foster, C. E. Scoffom, A. Barnett.

***Lines, Michael George,** B.Sc. (Wales). British. Near The Green, Cogenhoe, Northampton. Student. *Signed by :* S. Peat, W. R. Angus, F. H. Newth.

***Littlewood, Anthony Blair.** British. 4/22, Emperor's Gate, S.W.7. Student at Merton College, Oxford. *Signed by :* G. G. Coker, S. G. Phillips, P. V. Clifton.

Lovett, Martin, B.Sc. (Lond.), F.R.I.C. British. West Riding Rivers Board, 71, Northgate, Wakefield. Chief Inspector. *Signed by :* J. H. Garner, G. Brearley, H. H. Goldthorpe.

***Lynch, Eric Royle,** B.Sc. (Lond.). British. 10, Thorpe Street, Walkden, near Manchester. Student at University College, Exeter. *Signed by :* K. Schofield, S. J. Gregg, H. T. S. Britton.

Lynch, Sybil Bridget Roche, B.Sc. (Lond.), A.R.C.S., A.R.I.C. British. 81, Sussex Place, Slough. Assistant Lecturer, King's College of Household and Social Science. *Signed by :* H. Burton, A. Jackman, H. B. Hopkins, M. J. Birchenough.

McCarthy, The Rev. Jeremiah Patrick, M.A. (Oxon.), F.R.I.C. British. Ricci Hall, 93, Pokfulam Road, Hong Kong. R. C. Priest. *Signed by :* T. S. Wheeler, G. Bernfeld, V. G. Barry.

***Maniece, William Denis,** M.Sc. (Q.U.B.), A.R.I.C. British. Bloomsbury House Club, 34, Cartwright Gardens, W.C.1. Scientific Officer, Department of Government Chemist. *Signed by :* F. R. Ennos, P. M. Mooney, P. McGregor.

Marrian, Stanley Frederic, B.Sc. and Ph.D. (Glas.), F.R.I.C. British. Blackwood, Morton & Sons, Ltd., BMK Works, Finaghy, Belfast. Research Chemist. *Signed by :* R. G. R. Bacon, H. Graham, C. L. Wilson.

Marshall, George Reginald, B.Sc. (Lond.), F.R.I.C. British. 84, Fruen Road, Feltham. Chief Chemist, The Metafiltration Co., Ltd. *Signed by :* J. A. Pickard, H. J. T. Ellingham, R. L. Collett.

***Meston, Alexander Marshall,** B.Sc. (Aberd.), A.R.I.C. British. 15, Raeden Avenue, Aberdeen. Research Student. *Signed by :* R. M. Barrer, R. H. Thomson, J. M. C. Thompson.

Moser, Carl Mathew, A.B. (Indiana), M.S. (Wisconsin), Ph.D. (Harvard). American. Department of Chemistry, The Johns Hopkins University, Baltimore 18, Maryland, U.S.A. Instructor. *Signed by :* D. H. Andrews, E. B. Reid, N. A. Patrick.

***Newton, Stanley.** British. 82, Blenheim Road, Breightmet, Bolton. Laboratory Assistant. *Signed by :* R. J. W. Reynolds, E. M. Stoddart, R. N. Bate.

Owen, Clifford Alfred, M.A. (Cantab.), A.R.I.C. British. 1, Beconsfield Road, Dentons Green, St. Helens. Development Chemist. *Signed by :* P. Brown, G. W. Groves, K. T. Chapman.

***Packer, Robert Kenneth,** B.Sc. (Lond.). British. 85, Old Tiverton Road, Exeter. Research Student. *Signed by :* K. J. Hill, H. T. S. Britton, S. J. Gregg.

***Pain, David Lord,** B.Sc. (Lond.), A.R.C.S. British. 588, Southend Road, Elm Park. Research Chemist, May and Baker, Ltd. *Signed by :* J. N. Ashley, D. D. Libman, A. W. Nineham.

Parke, Dennis Vernon, B.Sc. (Lond.), A.R.I.C. British. 440A, Romford Road, Forest Gate, E.7. Assistant Lecturer in Biochemistry at St. Mary's Hospital Medical School. *Signed by :* R. T. Williams, G. King, J. N. Smith.

***Parker, Kenneth John.** British. 314, Blossomfield Road, Solihull, near Birmingham. Student at Oxford University. *Signed by :* E. J. Bowen, B. B. Goalby, F. M. Brewer.

***Parsons, Albert Keith.** British. Pilstye Farm, Cuckfield. Student. *Signed by :* F. G. Mann, P. Sykes, B. Lythgoe.

Paulson, Roy. British. 83A, Spencer Road, Belper. Paint Chemist. *Signed by :* E. D. Gilbert, A. G. Catchpole, N. Smith.

***Pendleton, Alan George,** B.Sc.Tech. (Manc.). British. 16, Kirkby Avenue, Sale. Demonstrator at Manchester College of Technology. *Signed by :* J. Kenner, G. Baddeley, A. Burawoy.

***Phillips, Glyn Owain,** B.Sc. (Wales). British. 9, Smith Street, Rhos, Wrexham. Research Student at U.C.N.W., Bangor. *Signed by :* S. Peat, W. R. Angus, F. H. Newth.

Pirt, Stanley John, B.Sc. (Wales). British. Department of Chemistry, University College of N. Wales, Bangor. Research Student. *Signed by :* S. Peat, W. R. Angus, W. J. Whelan.

Pritchett, Ervin Garrison, M.A. (Johns Hopkins). American. 904, Calwell Road, Baltimore, 29, Maryland, U.S.A. Student at The Johns Hopkins University. *Signed by :* E. B. Reid, W. A. Patrick, D. A. Andrews.

***Ranken, Michael David,** B.Sc.Tech. (Manc.). British. 45, Grange Valley, Haydock, St. Helens. R.A.F. Education Branch. *Signed by :* J. Kenner, G. Baddeley, T. K. Walker, A. F. H. Ward, N. Blakebrough.

Ratner, Benjamin Max, B.Sc. (Lond.), A.R.C.S., A.R.I.C. British. 86, Broadfields Avenue, Edgware. Senior Control Chemist. *Signed by :* H. Barany, M. Pianka, H. Warson.

Rea, Allan Arthur, F.R.I.C. British. Research Department, Ferodo Ltd., Chapel-en-le-Frith, via Stockport. Organic Chemist. *Signed by :* P. D. Ritchie, J. C. C. Ransom, E. W. Mills.

***Rich, Frank Reginald.** British. 28, Brandville Road, West Drayton. Chemist at Metaplast (England), Ltd. *Signed by :* G. J. Hills, J. F. Herringshaw, B. Atkinson.

Rigby, Alan James Eckersley, B.A. (Cantab.). British. Queen's College, Cambridge. Student. *Signed by :* P. Maitland, F. G. Mann, B. Lythgoe.

***Robinson, Donald,** B.Sc. (L'pool). British. 55, Rothesay Avenue, Greenford. Assistant Lecturer, Biochemistry Department, St. Mary's Hospital Medical School, W.2. *Signed by :* G. King, J. N. Smith, R. T. Williams.

Ruby, William Raymond, M.A. (Johns Hopkins). American. 1317, West Forty-First Street, Baltimore 11, Maryland, U.S.A. Research Student. *Signed by :* E. B. Reid, D. H. Andrews, W. A. Patrick.

Ruxton, David, B.Pharm. British. c/o 12, Devanha Gardens, Aberdeen. *Signed by :* M. W. Partridge, F. C. Cooper, C. C. Addison.

Skinner, Henry Alistair, B.A., B.Sc., and D.Phil. (Oxon.). British. 43, Daisy Bank Road, Victoria Park, Manchester, 14. Lecturer in Chemistry at Manchester University. *Signed by :* A. E. Gillam, M. G. Evans, J. B. M. Herbert.

Slates, Harry Lovell, M.Sc. (Ohio). American. 30, Spruce Street, Cranford, New Jersey, U.S.A. Chemist at Research and Development Division, Merck & Co., Inc. *Signed by :* M. Tishler, W. L. Mosby, E. M. Chamberlin.

Sletzinger, Meyer, M.A. and Ph.D. (Columbia). American. 110—31, 73 Road, Forest Hills, Long Island, N.Y., U.S.A. Senior Research and Development Chemist at Merck & Co., Inc. *Signed by :* C. R. Addinall, M. Tishler, E. M. Chamberlin.

***Small, Norman James Herbert,** M.Sc. (Q.U.B.). British. 19, Ardlee Avenue, Holywood, Co. Down. Research Student. *Signed by :* H. Graham, A. R. Ubbelohde, C. L. Wilson.

***Smith, Peter,** B.Sc. (Lond.), A.R.C.S. British. 128, Widdenham Road, N.7. Research Student at the Royal College of Science. *Signed by :* L. N. Owen, R. P. Linstead, F. E. Humphries.

Soane, Oscar Vincent, B.Sc. (Glas.), F.R.I.C. British. Barry, Ostlere & Shepherd, Ltd, Kirkcaldy, Fife. Chemist with Barry, Ostlere & Shepherd, Linoleum Manufacturers. *Signed by :* H. Baines, E. B. Knott, S. C. Goddard, K. J. Reed.

* **Somerville, Anthony William,** B.Sc. (Manc.). British. 81, Ostrich Lane, Heaton Park, Prestwich. Research Student at Manchester University. *Signed by :* T. H. H. Quibell, C. Campbell, E. R. H. Jones.

***Stevens, John William.** British. 3, County Gate, New Eltham, S.E.9. Student. *Signed by :* P. J. Pengilly, H. E. Cox, J. D. Cox.

Stones, William Frederick, A.R.I.C. British. 75, Finsbury Avenue, Walker Estate, Newcastle-on-Tyne, 6. Consulting and Analytical Chemist. *Signed by :* E. J. Smith, G. A. Swan, A. F. Daglish.

Swaddle, Donald, B.Sc. (Lond.), A.R.I.C. British. The Cottage, Duncote, Towcester, Northants. Research Chemist. *Signed by :* W. Siddall, D. R. Bell, G. F. Rice.

Terleski, John Theodore, B.Sc.Tech. (Manc.), Ph.D. (L'pool), A.R.I.C. British. 1, Wood Road, Brooklands, Sale. Managing Director. *Signed by :* T. P. Hilditch, W. F. Williams, G. Ogden.

***Thomas, Alan Francis.** British. Wadham College, Oxford. Student. *Signed by :* W. A. Waters, M. C. Ford, D. H. Derbyshire.

***Thomas, Gwen Jean,** B.Sc. (Wales). British. Glegyrog Ganol, Rhosgoch, Anglesey. Research Student. *Signed by :* S. Peat, W. R. Angus, W. J. Whelan.

Tizard, Anthony Noel, B.Sc. (Lond.), A.R.I.C. British. Browndown, Ewell Road, Cheam. Chemist, Anglo-Iranian Oil Co. *Signed by :* N. Lindop, W. J. Hickinbottom, C. M. French.

***Warren, David Ronald de Mey,** B.Sc. (Sydney). Australian. 39, Russell Road, Kensington, W.14. Student. *Signed by :* A. J. Everett, J. H. Burgoyne, A. C. Egerton.

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" The kinetics of halogen substitution. Part VIII. Halogen addition. Part XV. Benzyl and allyl chloride, bromide, and cyanide." By L. D. Swindale, B. E. Swedlund, and P. W. Robertson.

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" Steroids and the Walden inversion. Part VI. Reduction of cholest-5-en-3-one with lithium aluminium hydride." By C. W. Shoppee and G. H. R. Summers.

" Aminoalkyl tertiary carbinols and derived products. Part II. 3-Amino-1 : 1-di-2′-thienylalkan-1-ols and -alk-1-enes." By D. W. Adamson.

" The nitration of polystyrene." By H. Zenftman.

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" The preparation of a series of (±)-*n*-eicosanols and *n*-eicosanones." By Vivienne R. Churchward, N. A. Gibson, R. J. Meakins, and Joan W. Mulley.

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" The chemistry of fungi. Part X. The synthesis of 4-hydroxy-3-acetylcoumarins." By G. G. Badcock, F. M. Dean, Alexander Robertson, and W. B. Whalley.

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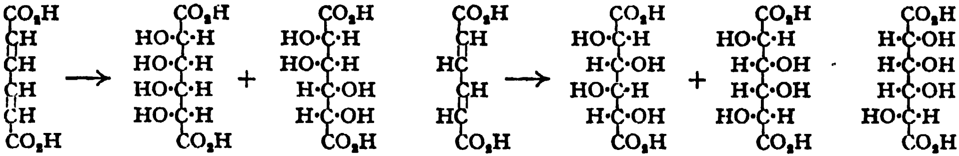
later) could give, on ring-fission, not only *allo*mucic acid (V) but also mucic (VIII), DL-mannosaccharic (VI and enantiomorph), and DL-talomucic (IX and enantiomorph) acids, and there was no indication of the formation of such a complex mixture of hexahydroxyadipic acids.



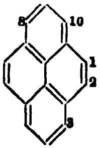
$$\begin{array}{c}CO_2H\\CH\\CH\\CH\\CH\\CO_2H\end{array}\longrightarrow\begin{array}{c}CO_2H\\HO\cdot C\cdot H\\HO\cdot C\cdot H\\HO\cdot C\cdot H\\HO\cdot C\cdot H\\CO_2H\end{array}+\begin{array}{c}CO_2H\\HO\cdot C\cdot H\\HO\cdot C\cdot H\\H\cdot C\cdot OH\\H\cdot C\cdot OH\\CO_2H\end{array}\qquad\begin{array}{c}CO_2H\\CH\\HC\\CH\\HC\\CO_2H\end{array}\longrightarrow\begin{array}{c}CO_2H\\HO\cdot C\cdot H\\H\cdot C\cdot OH\\HO\cdot C\cdot H\\H\cdot C\cdot OH\\CO_2H\end{array}+\begin{array}{c}CO_2H\\HO\cdot C\cdot H\\H\cdot C\cdot OH\\H\cdot C\cdot OH\\HO\cdot C\cdot H\\CO_2H\end{array}\qquad\begin{array}{c}CO_2H\\H\cdot C\cdot OH\\H\cdot C\cdot OH\\H\cdot C\cdot OH\\HO\cdot C\cdot H\\CO_2H\end{array}$$

(III.) (V.) (VI.) (IV.) (VII.) (VIII.) (IX.)

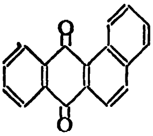
This degradation of benzene by oxidation with the Milas reagent is of interest in connection with the metabolic conversion of benzene into *trans-trans*-muconic acid (IV), which is possibly an artefact formed by isomerisation of the *cis-cis*-acid (III) which should be the primary product of ring fission (Jaffé, *Z. physiol. Chem.*, 1909, **62**, 58; Drummond and Finar, *Biochem. J.*, 1938, **32**, 79; Bernhard and Greesley, *Helv. Chim. Acta*, 1941, **24**, 83). Such isomerisation is known to be readily effected (Grundmann and Trischmann, *Ber.*, 1936, **69**, 1755).

Naphthalene, Phenanthrene, Chrysene, Anthracene, and Pyrene.—The products formed from these hydrocarbons by oxidation with the Milas reagent call for little comment. In the case of naphthalene the only product isolated was phthalic acid, also obtained by Charrier and Moggi (*Gazzetta*, 1927, **57**, 736) by oxidation with hydrogen peroxide in an acid medium. Less extensive degradation occurs when naphthalene, α- or β-naphthol, or β-naphthaquinone is oxidised with peracetic acid, *o*-carboxy*allo*cinnamic acid being formed in each case (Böeseken and Slooff, *Rec. Trav. chim.*, 1930, **49**, 100; Böeseken and von Königsfeldt, *ibid.*, 1935, **54**, 313).

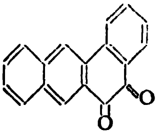
Phenanthrene gave *cis*-9 : 10-dihydroxy-9 : 10-dihydrophenanthrene, phenanthraquinone, and diphenic acid. Charrier and Moggi (*loc. cit.*) had obtained diphenic acid by oxidising phenanthrene with hydrogen peroxide in boiling acetic acid, a result which we confirmed. Chrysene was oxidised to 1 : 2-chrysaquinone, and anthracene to 9 : 10-anthraquinone, which are the normal products of oxidation with chromic acid. Pyrene (X) was rapidly attacked and after about a week the products were separated into a mixture of quinones which appeared to be the 3 : 8- and 3 : 10-quinones which are the normal oxidation products. When the action of the Milas reagent was prolonged for a year the product was naphthalene-1 : 4 : 5 : 8-tetracarboxylic acid, characterised as its *methyl* ester. There was no evidence of attack at the 1 : 2-positions of pyrene, which are the positions exclusively attacked when pyrene is treated with osmium tetroxide in benzene–pyridine (Cook and Schoental, *loc. cit.*).



(X.)



(XI.)



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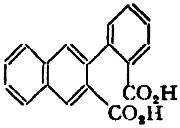
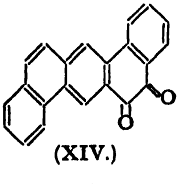
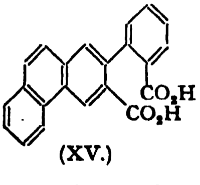


(XIII.)

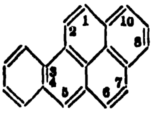
1 : 2-*Benzanthracene and* 1 : 2-5 : 6-*Dibenzanthracene.*—After a few days 1 : 2-benzanthracene gave the 3 : 4-quinone (XII) (isolated in 15% yield) and the 9 : 10-quinone (XI) (isolated in 20% yield). The *o*-quinone (XII), which is conveniently prepared in this way, is evidently formed through the intermediary of *cis*-3 : 4-dihydroxy-3 : 4-dihydro-1 : 2-benzanthracene (Cook and Schoental, *loc. cit.*), a small amount of which was isolated by chromatography. When 1 : 2-benzanthracene was heated on the water-bath with the reagent acidic products were formed more rapidly than in the cold. Phthalic acid and 2-*phenylnaphthalene*-3 : 2′-*dicarboxylic acid* (XIII) were isolated, and there was also evidence of the formation of keto-acids.



(XIV.)



(XV.)



(XVI.)

With 1 : 2-5 : 6-dibenzanthracene the reaction took a similar course. On account of the low solubility of the hydrocarbon a more dilute solution was used, and the reaction was very sluggish at room temperature. When the reactants were heated on the water-bath the dark red 1 : 2-5 : 6-dibenzanthra-3 : 4-quinone (XIV) separated after a few days and was isolated in 35% yield. From the liquors the 9 : 10-quinone was also isolated and, in addition, 2-phenylphenanthrene-3 : 2′-dicarboxylic acid (XV), which was also obtained directly from the *o*-quinone (XIV) by oxidation with alkaline hydrogen peroxide.

3 : 4-*Benzpyrene* (XVI).—This was readily oxidised and the solution became deep-red. A mixture of quinones was then separated from other products of oxidation by chromatography on alumina. These quinones did not account wholly for the intensity of colour (noted also in the case of some of the other hydrocarbons). Possibly the high colour intensity was due to formation of hydroxylated quinones. Warren (*Biochem. J.*, 1943, **37**, 338), who studied the atmospheric oxidation of aqueous acetone solutions of 3 : 4-benzypyrene in presence of ascorbic acid, also observed the formation of deeply coloured products in addition to known quinones.

Chromatography of the quinone fraction from benzpyrene resulted in only partial separation and the individual constituents were not isolated. Evidence was obtained, however, of the presence of the known 5 : 8- and 5 : 10-quinones (Vollmann *et al.*, *Annalen*, 1937, **531**, 1) and of a new *o*-quinone. The latter is probably 3 : 4-*benzpyrene*-6 : 7-*quinone*, which was prepared for comparative purposes by oxidation of the dihydroxydihydro-3 : 4-benzpyrene of Cook and Schoental (*loc. cit.*), and characterised by formation of a *quinoxaline* by reaction with *o*-phenylenediamine. The diol is believed to be the 6 : 7-diol, although the alternative 1 : 2-structure is not excluded (see numbering on formula XVI).

Oxidation of 1 : 2-*Benzanthracene with Hydrogen Peroxide in Absence of Osmium Tetroxide.*—These experiments were carried out for comparison with the action of the Milas reagent. A solution of the hydrocarbon in acetone and *tert.*-butanol containing hydrogen peroxide remained unchanged for several weeks when kept in the dark. If methylamine hydrochloride was also present (used as a source of chloride ions) then oxidation took place and after two months a considerable proportion of the hydrocarbon had been oxidised to 1 : 2-benzanthra-9 : 10-quinone (XI) and phthalic acid. There was no evidence of the formation of the 3 : 4-quinone (XII). A similar result was obtained when haematin was used in place of methylamine hydrochloride.

DISCUSSION.

The results of this investigation are mainly of interest on account of the additional evidence which they furnish as to the mechanism of oxidation by the Milas reagent, and they also perhaps provide one further span towards bridging the gap between biochemical and purely chemical oxidation of the aromatic hydrocarbons. Our earlier results with Criegee's osmium tetroxide reagent showed that it is possible to bring about selective chemical attack at positions in the molecules of polycyclic aromatic hydrocarbons which are not normally the most reactive. They also showed how it is possible to simulate the " perhydroxylation " reactions which are a characteristic feature of several of the biochemical oxidations. The positions attacked by osmium tetroxide are not those at which biochemical hydroxylation takes place, but in this connection it has been postulated that combination between the hydrocarbon and the oxidising enzyme may immobilise some of the more reactive centres in the hydrocarbon molecule.*

The diols and the related phenols which have been isolated in metabolic experiments represent only a small proportion of the hydrocarbon administered, and it is clear that most of the material undergoes more extensive degradation. Except in the case of benzene (see above) the products of this degradation have not been identified. Using 1 : 2-5 : 6-dibenzanthracene containing isotopic carbon, Heidelberger and his collaborators (*Cancer*, 1948, **1**, 252, 261) have shown that acids are formed by ring-fission of the hydrocarbon and also that some of the material is completely oxidised to carbon dioxide. Metabolic studies by one of us (R. S.) with chrysene, 1 : 2-benzanthracene, 1 : 2-5 : 6-dibenzanthracene, and 3 : 4-benzpyrene have likewise indicated that in all these cases acidic degradation products of the hydrocarbons are present in the excreta of the animals. To this extent oxidation by the Milas reagent imitates the metabolic oxidation, for prolonged treatment with the reagent always led to extensive conversion of the hydrocarbons into acidic degradation products, only some of which have been identified.

There remains the question as to how far the chemical perhydroxylations really follow the pattern of the corresponding biochemical processes. Osmium tetroxide oxidation of olefins and of phenanthrene has been shown by Criegee (*loc. cit.*) to give *cis*-diols through the intermediary of cyclic osmic esters. It is quite conceivable that metallic catalysts could function in a similar way in biochemical " perhydroxylation." But if it can be shown that one method of oxidation consistently gives *cis*-diols and the other *trans*-diols, then it is a reasonable inference that the reaction mechanisms are different. It is for this reason that great importance attaches to the determination of the configurations of the metabolic diols, and as already stated, evidence is accumulating that these are *trans*-isomers. An alternative possibility is that biochemical perhydroxylation is effected by free hydroxyl radicals, and there is much current opinion in favour of the view that free radicals play an important role in biological oxidations (see Waters, " Chemistry of Free Radicals," Oxford, 1946, p. 259; LuValle and Goddard, *Quart. Review Biol.*, 1948, **23**, 197).

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* Berenblum and Schoental (*Cancer Res.*, 1943, **3**, 686) pointed out that in the cases of 1 : 2-benzanthracene and 1 : 2-5 : 6-dibenzanthracene the positions of the molecules where metabolic oxidation occurs are those at which sulphonation takes place *in the corresponding quinones*. This has been misinterpreted by Neish (*Biochem. J.*, 1948, **43**, 534) who states, incorrectly, that Berenblum and Schoental observed that benzanthracene and dibenzanthracene are metabolically attacked at points where sulphonation *of these hydrocarbons* occurs.

Milas (*J. Amer. Chem. Soc.*, 1937, **59**, 2342) was inclined to regard oxidation by osmium tetroxide-catalysed hydrogen peroxide as involving attack by free hydroxyl radicals, formed by the action of perosmic acid on hydrogen peroxide, as in its dissociation by light (compare Spring, *Ann. Reports*, 1943, **40**, 108). That free hydroxyl radicals can oxidise benzene to phenol was shown by Stein and Weiss (*Nature*, 1948, **161**, 650; cf. Loebl, Stein, and Weiss, *J.*, 1949, 2074), who found phenol among the products of the action of *X*-rays on water and benzene. To this extent the Milas reagent produces the same result as free hydroxyl radicals. Moreover, Milas, Kurz, and Anslow (*J. Amer. Chem. Soc.*, 1937, **59**, 543) observed the oxidation of maleic acid to *meso*tartaric acid by hydrogen peroxide in presence of light and attributed this to addition of free hydroxyl radicals. This *cis*-addition rather than the *trans*-addition which might have been expected by such a mechanism excited no comment. Recently, Merz and Waters (*J.*, 1949, S 15) have shown that free hydroxyl radicals, produced by the action of ferrous salts on aqueous hydrogen peroxide, do not add to the double bond of maleic and fumaric acids. Hence the photochemical oxidation of maleic acid is not to be ascribed to the action of free hydroxyl radicals.

The same type of argument may be adduced to show that the perhydroxylation of double bonds by hydrogen peroxide in presence of osmium tetroxide is not due to the action of free hydroxyl radicals. It is true that in the Milas reagent part of the hydrogen peroxide is present as *tert.*-butyl hydroperoxide (compare Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205; Criegee and Dietrich, *Annalen*, 1948, **560**, 135), and that an alkyl hydroperoxide has been shown to break down to give free radicals (Robertson and Waters, *Trans. Faraday Soc.*, 1946, **42**, 201; *J.*, 1948, 1578). But the Milas reagent does not normally bring about the extensive degradations which Merz and Waters (*loc. cit.*) observed with free hydroxyl radicals; it does effect perhydroxylation of the double bonds in compounds of the maleic acid type, and moreover the method leads to *cis*-addition to the double bond (Milas and Sussman, *J. Amer. Chem. Soc.*, 1937, **59**, 2345; Milas, Sussman, and Mason, *ibid.*, 1939, **61**, 1844). It is clear, in fact, that the oxidation involves the intermediate formation of cyclic osmic esters, as in the Criegee method in which such esters are isolated.

Our own results with polycyclic hydrocarbons show that in part oxidation at a " potential " double bond takes place by the same mechanism. The isolation of *cis*-α-diols from phenanthrene and 1 : 2-benzanthracene, with no evidence of the presence of stereoisomeric *trans*-diols, points clearly to the intermediate formation of cyclic osmic esters. These diols undoubtedly represent the first stage also in the reactions which lead to 1 : 2-benzanthra-3 : 4-quinone (XII) and the acid (XIII) from 1 : 2-benzanthracene and the allied compounds (XIV) and (XV) from 1 : 2-5 : 6-dibenzanthracene. Moreover, the quite appreciable amounts of these products isolated indicate that the reactions by this route represent a considerable proportion of the whole. However, quite a different mechanism must operate in the oxidation of anthracene, 1 : 2-benzanthracene, and 1 : 2-5 : 6-dibenzanthracene to the 9 : 10-quinones (*e.g.*, XI), and in the oxidation of pyrene and 3 : 4-benzpyrene to their heteronuclear quinones. These oxidations may be due to the action of free hydroxyl radicals formed by dissociation of hydrogen peroxide, but there is no evidence bearing on this point, and judgment must be reserved. We are extending this work to study the effect on polycyclic hydrocarbons of free hydroxyl radicals and also of hydrogen peroxide in the presence of other catalysts. In this connection, it may be noted that Sequin (*Compt. rend.*, 1943, **216**, 667) obtained only the *trans*-α-glycol by oxidising *cyclo*hexene with hydrogen peroxide in acetone, in presence of selenium dioxide. A similar result was reported by Treibs (*Angew. Chem.*, 1939, **52**, 698) with pervanadic acid as catalyst.

EXPERIMENTAL.

General.—A solution of the hydrocarbon (0·001 g.-mol.) in acetone was treated with a stock solution of hydrogen peroxide (2—10 c.c.), prepared by diluting 90% hydrogen peroxide to 20—40% with *tert.*-butanol, and with a 1—2% solution of osmium tetroxide in *tert.*-butanol, so that the final concentration of the tetroxide varied between 0·01% and 0·5%. The solution was kept in a stoppered flask at room temperature in diffused light. Addition of the *tert.*-butanol solutions usually resulted in partial separation of the crystalline hydrocarbons, but the crystals redissolved in the course of the reaction. The colourless solutions slowly developed yellow or red colours of increasing intensity. There was usually an induction period when highly purified material was used. After the hydrogen peroxide initially added had been consumed the osmium tetroxide became reduced so that the solution became almost black. This colour was discharged by addition of more hydrogen peroxide solution. The rapidity with which this darkening of colour occurred furnished an index of the rate of oxidation of the hydrocarbons except in the cases of pyrene and 3 : 4-benzpyrene when very dark oxidation products were formed and the dark colour then persisted for some months. In view of the complex mixtures of oxidation products formed and the difficulty of isolating individual constituents a quantitative study was not attempted. Yields are recorded only when reaction products actually crystallised from solution.

For isolation of the products, any solid which had separated was collected, and the filtrate concentrated under reduced pressure at 40—50°. By this means solvents, osmium tetroxide, and volatile products were removed. Colourless crystals which collected in the still-head and condenser were identified as the trimeric cyclic peroxide of acetone, m. p. 94—95° (Wolffenstein, *loc. cit.*). Attempts to isolate the products without this preliminary concentration resulted in formation of dark colloidal suspensions of lower oxides of osmium, and as far as could be judged the distillation process did not bring about any alteration in the oxidation products.

The residue after distillation was a yellow or brownish viscous oil, which was treated with dilute sodium hydrogen carbonate solution and extracted with benzene. Dark resinous material remained insoluble in both phases, but dissolved when sodium hydroxide solution was added, after removal of the sodium hydrogen carbonate layer. Acidification of the dark sodium hydroxide extracts gave brownish material which did not crystallise and gave no crystalline derivatives by reductive methylation or acetylation.

The benzene extracts were submitted to chromatography on alumina and were thus separated into unchanged hydrocarbon, diol (in two cases), and quinones. In all cases highly coloured zones of strongly adsorbed material were visible on the upper part of the column, but pure products could not be obtained after these were eluted with acidified alcohol.

The sodium hydrogen carbonate extract was acidified, and the resulting acids separated by fractional crystallisation from various solvents or by vacuum distillation of their methyl esters, formed by treatment with ethereal diazomethane.

Benzene.—Two parallel experiments were made. In one, the reaction was carried out in acetone solution, as in the other cases recorded in this paper. In the other, *tert.*-butanol alone was used as solvent. Oxidation took place more rapidly in acetone solution, but in both cases the same products were isolated. The reaction mixtures, prepared in each case by using 10 c.c. of benzene, became yellow in a few days and phenol was detected by its smell, by the preparation of tribromophenol, m. p. 93°, from a sample of distillate, and by the blue colour given with 2 : 6-dichloroquinonechloroimide in neutral or alkaline solution (Porteous and Williams, *Biochem. J.*, 1949, **44**, 56).

The colour of the solution of reactants deepened on storage, but after some months, during which several additions of hydrogen peroxide solution were made, the colour became pale yellow and a white precipitate was formed. This (35 mg.) was recrystallised from hot water and formed a microcrystalline powder which decomposed at 197°. Analysis showed the compound to be a tetrahydroxyadipic acid (Found : C, 34·0; H, 5·0. Calc. for $C_6H_{10}O_8$: C, 34·3; H, 4·8%). Its ethyl ester, prepared by heating it under reflux with ethanol containing a few drops of concentrated hydrochloric acid, had m. p. *ca.* 150°. These data are in approximate agreement with those given for *allo*mucic acid by Posternak (*Helv. Chim. Acta*, 1935, **18**, 1283) (acid, m. p. 197—198°; ethyl ester, m. p. 153—154°) and by Lapsley, Robertson, and Patterson (*J.*, 1940, 862) (acid, m. p. 199—200°; ethyl ester, m. p. 155°). Through the kindness of Mr. J. Robertson, who generously gave us a sample of *O*-tetra-acetyl*allo*mucic acid prepared by the method described by himself and his collaborators, we have been able to establish that our oxidation product is in fact *allo*mucic acid. The methyl ester of our acid had m. p. 170° and gave an *O*-tetra-acetyl derivative, m. p. 204—206°. The m. p.s of the acid and its three derivatives were not depressed by mixing with the acid (prepared by acid hydrolysis of the authentic *O*-tetra-acetyl*allo*mucic acid) and its corresponding derivatives. On the other hand, a mixture of the methyl ester of the tetra-acetate of our acid and methyl *O*-tetra-acetylmucate, m.p. 196—197° (Simon and Guillaumin, *Compt. rend.*, 1924, **179**, 1324), melted at 180—196°. Pure *methyl* allo*mucate* formed transparent prisms (from methanol), m. p. 175° after softening (Found : C, 40·6; H, 5·9. $C_8H_{14}O_8$ requires C, 40·3; H, 5·9%). *Methyl* O-*tetra-acetyl*allo*mucate*, prepared from methyl *allo*mucate by acetylation with acetic anhydride, formed transparent rhombic prisms, m. p. 205—206° (Found : C, 47·3; H, 5·6. $C_{16}H_{22}O_{12}$ requires C, 47·3; H, 5·5%).

In another experiment, a mixture of benzene (10 c.c.) and acetone (10 c.c.) was treated with 2% osmium tetroxide (2 c.c.) and 40% hydrogen peroxide (60 c.c.), both in *tert.*-butanol. After nine months the filtered solution was concentrated under reduced pressure at 40—50°. A solution in water of the residual oil was partly neutralised with sodium carbonate and the solution heated under reflux for 2½ hours with *p*-bromophenacyl bromide (0·5 g.) in ethanol (10 c.c.). After concentration and cooling the resulting *p*-bromophenacyl ester was recrystallised from ethanol and formed glistening leaflets, m. p. 198—200°. This was shown to be p-*bromophenacyl* meso*tartrate*, a sample of which was prepared from authentic *meso*tartaric acid and had m. p. 198—200°, alone or mixed with the above product (Found : C, 44·25; H, 3·2. $C_{20}H_{16}O_8Br_2$ requires C, 44·1; H, 3·0%).

In yet another experiment the filtrate from the crude *allo*mucic acid was concentrated under reduced pressure, the residue dissolved in water and almost neutralised with sodium hydroxide, and the boiling solution then treated with saturated calcium acetate solution. Without cooling, the white precipitate was collected, washed, and dried. It was shown by titration with warm acid permanganate solution to consist of calcium oxalate. The filtrate was concentrated and gave large crystals which were redissolved in hot water; the solution was acidified and then extracted with ether. After removal of the ether the residue was treated with ethereal diazomethane and gave colourless prisms, m. p. 111—112°, shown by mixed m. p. to consist of methyl *meso*tartrate.

In yet another experiment, the crude mixture of acids, freed from volatile substances, was esterified with diazomethane and the esters were distilled. The fraction, b. p. 110°/0·3 mm., gave again methyl *meso*tartrate. The higher-boiling esters could not be separated; much of the material underwent decomposition during distillation. Although the hydroxyl groups of *meso*tartaric acid were not affected by diazomethane it may be noted that Schmidt and Zeiser (*Ber.*, 1934, **67**, 2120) found that tartaric and other hydroxy-acids undergo etherification as well as esterification with diazomethane.

Naphthalene.—A solution of the hydrocarbon (5 g.) in acetone (25 c.c.) with 1% osmium tetroxide in *tert.*-butanol (2·5 c.c.) and hydrogen peroxide solution (15 c.c.) immediately became yellow and oxidation proceeded rapidly; further quantities of hydrogen peroxide solution were added as required. After 18 days the solution was worked up in the usual way. The acidic fraction was mainly soluble in water. It was extracted with ether, recovered from the extract, and recrystallised several times from ethyl acetate and aqueous methanol. The resulting acid had m. p. *ca.* 200°, and on sublimation gave long needles, m. p. 137°, shown by mixed m. p. to be phthalic anhydride.

When the solution of the reactants was worked up after shorter periods there were shown to be present phenolic material and also coloured neutral products, probably naphthaquinones (compare Milas, U.S.P., 2,395,638).

Phenanthrene.—The hydrocarbon (3 g.) in acetone (15 c.c.) was treated with the Milas reagent (2 c.c. of osmium tetroxide solution and 10 c.c. of hydrogen peroxide solution) at room temperature. Further additions of hydrogen peroxide solution were made from time to time, about 60 c.c. of a 20% solution being used in all. After 26 days the red solution was concentrated *in vacuo* and then deposited crystals (55 mg.), m. p. 204—206°, which were shown to consist of phenanthraquinone. The filtrate was worked up in the usual way, and on passing the benzene solution through a column of alumina there were obtained from the first benzene filtrate some unchanged phenanthrene and then a fraction which gave fine colourless needles (from light petroleum) of *cis*-9 : 10-dihydroxy-9 : 10-dihydrophenanthrene (25 mg.), m. p. 178° alone or mixed with a specimen prepared as described by Criegee, Marchand, and Wannowius (*Annalen*, 1942, **550**, 99). A yellow zone was cut from the alumina column and gave on elution with benzene more phenanthraquinone, m. p. 206—207°.

The acidic fraction was repeatedly crystallised from aqueous methanol and ethyl acetate. This gave colourless prisms, m. p. 228—230°, shown by mixed m. p. to be diphenic acid. Identification was completed by conversion into the anhydride, m. p. and mixed m. p. 217°. The sodium hydroxide extract on acidification gave a product which was purified by passing its benzene solution through a column of alumina. This gave a small amount of 9-phenanthrol, m. p. and mixed m. p. 148°.

Chrysene.—In this case reaction was slow, but the hydrocarbon in suspension (using 330 mg. in 50 c.c. of acetone) dissolved during the course of 3 weeks. The red solution was concentrated *in vacuo* and gave red needles of 1 : 2-chrysaquinone, m. p. 237—238°, not depressed by mixing with an authentic specimen. Small amounts of acidic and other products were also formed.

Anthracene.—The hydrocarbon (100 mg.) in acetone (10 c.c.) was treated with 1% osmium tetroxide solution (1 c.c.) and 20% hydrogen peroxide solution (2 c.c.). After 4 days long needles of anthraquinone began to separate (m. p. and mixed m. p. 275°). In another experiment 250 mg. of anthracene gave, after 4 months, 170 mg. of anthraquinone and traces of unidentified acidic products.

Pyrene.—A solution of this hydrocarbon (350 mg.) in acetone (10 c.c.) became pink immediately on the addition of the Milas reagent. After a week the deep-red solution was worked up. Chromatography of the benzene extract led to recovery of some unchanged hydrocarbon and gave several coloured bands. Chloroform eluted a mixture of quinones, which were not completely separated by repeated chromatography in benzene. The colours given by the various fractions with concentrated sulphuric acid indicated the presence of the 3 : 8- and 3 : 10-quinones (Vollmann *et al.*, *loc. cit.*). There was no definite evidence of the presence of the 1 : 2-quinone.

In another experiment the solution of reactants was kept for about a year. The deep colour slowly faded and a pale yellow solid was deposited. This was recrystallised from much ethanol and then sublimed under reduced pressure, giving yellowish needles of naphthalene-1 : 4 : 5 : 8-tetracarboxylic dianhydride, m. p. above 360°. Treatment of the silver salt with methyl iodide gave the *methyl* ester as colourless leaflets, m. p. 196—198°, not depressed by mixture with a sample similarly prepared from Cook and Hewett's tetracarboxylic acid (*J.*, 1933, 405) (Found : C, 60·2; H, 4·7. $C_{18}H_{16}O_8$ requires C, 60·0; H, 4·5%).

1 : 2-*Benzanthracene.*—(*a*) A solution of the hydrocarbon (0·5 g.) in acetone (20 c.c.) was treated with 40% hydrogen peroxide (2 c.c.) and 1% osmium tetroxide (1 c.c.), both in *tert.*-butanol. The solution soon became red and in the course of 3—4 days red crystals separated (80 mg.). After crystallisation from chloroform these had m. p. 260—262°, not depressed by admixture with a sample of the quinone (XII) prepared by chromic acid oxidation of *cis*-3 : 4-dihydroxy-3 : 4-dihydro-1 : 2-benzanthracene. The product gave a purple solution in concentrated sulphuric acid, in agreement with Fieser and Dietz (*J. Amer. Chem. Soc.*, 1929, **51**, 3141). The quinone reacted with *o*-phenylenediamine in acetic acid solution to give the *quinoxaline* as pale yellow needles, m. p. 256—257° (Found : C, 86·9; H, 4·3. $C_{24}H_{14}N_2$ requires C, 87·2; H, 4·3%).

The mother-liquors from which this quinone had been separated were worked up in the normal manner. Chromatography of the benzene extract showed that very little unchanged hydrocarbon was present. The benzene eluate gave 1 : 2-benzanthra-9 : 10-quinone (XI) (120 mg.) as orange needles, m. p. 167—168°. Chromatographic purification of the material from the mother-liquors of this gave a small amount of *cis*-3 : 4-dihydroxy-3 : 4-dihydro-1 : 2-benzanthracene, m. p. 201—205°, not depressed by admixture with a sample prepared as described by Cook and Schoental (*loc. cit.*).

The acidic products insoluble in water (*i.e.*, precipitated by acidification of the sodium hydrogen carbonate extract) were recrystallised several times from ethyl acetate and gave a small amount of colourless crystals, m. p. 245°. This acid was shown to be identical with 2-*phenylnaphthalene*-3 : 2′-*dicarboxylic acid* (XIII), colourless prisms, m. p. 249—250° (from ethyl acetate), formed by oxidation of 1 : 2-benzanthra-3 : 4-quinone (XII) with alkaline hydrogen peroxide (compare Weitz, Schobbert, and Seibert, *Ber.*, 1935, **68**, 1163), and the same acid was also formed from the quinone (XII) by treatment with the Milas reagent for several weeks (Found : C, 74·3; H, 4·1. $C_{18}H_{12}O_4$ requires C, 74·0; H, 4·1%). Its *methyl* ester, prepared by heating it with hydrochloric acid in methanol, formed colourless plates, m. p. 86—87·5° (Found : C, 75·05; H, 5·0. $C_{20}H_{16}O_4$ requires C, 75·1; H, 5·0%)

In another experiment on the oxidation of benzanthracene by the Milas reagent the acidic products were esterified with diazomethane and distilled *in vacuo*. The first fraction, b. p. 90—100°/0·3 mm., was mostly methyl phthalate, identified by conversion into the anhydride. The fraction, b. p. 120—180°/0·3 mm., gave on hydrolysis the acid (XIII). Treatment of the crude acid mixture with 2 : 4-dinitrophenylhydrazine gave a small amount of solid, indicating the presence of keto-acids, but a pure substance could not be isolated.

(*b*) 1 : 2-Benzanthracene (0·5 g.) in acetone (20 c.c.) was treated with 50% hydrogen peroxide in *tert.*-butanol (3 c.c.) and methylamine hydrochloride (140 mg.). The mixture was kept in the dark for 2 months and gave 1 : 2-benzanthra-9 : 10-quinone (170 mg.) and acidic products from which phthalic acid was isolated by distillation of the esterified material.

(*c*) A similar experiment with haematin (prepared from haemin as described by Fischer *et al.*, *Z. physiol. Chem.*, 1930, **193**, 156) in place of methylamine hydrochloride gave 1 : 2-benzanthra-9 : 10-quinone in 50% yield and some phthalic acid.

1 : 2-5 : 6-*Dibenzanthracene*.—The slight solubility of this hydrocarbon necessitated the use of a very dilute solution and the reaction was exceedingly slow at room temperature. It was therefore accelerated by heating. The hydrocarbon (500 mg.) in acetone (50 c.c.) was treated with 50% hydrogen peroxide (10 c.c.) and 1% osmium tetroxide (10 c.c.), both in *tert.*-butanol, and the solution was heated at 70° for 3—4 days. The purple crystals which separated (160 mg.) were recrystallised from acetic acid and formed dark red needles, m. p. 325°. This substance was shown to be identical with 1 : 2-5 : 6-dibenzanthra-3 : 4-quinone (XIV) prepared as described by Stephenson (*J.*, 1949, 2620), who gives m. p. 327—329° (compare Cook, *J.*, 1933, 1594). Concentration of the original filtrate gave a yellow solid which crystallised from benzene in orange-yellow needles, m. p. 246°, consisting of 1 : 2-5 : 6-dibenzanthra-9 : 10-quinone (Clar, *Ber.*, 1929, **62**, 350).

The sodium hydrogen carbonate fraction on acidification gave a solid precipitate which after several recrystallisations formed a cream microcrystalline powder (from acetone), m. p. 307—309°. This was 2-phenylphenanthrene-3 : 2′-dicarboxylic acid (XV), a sample of which was prepared for comparison by oxidation of the quinone (XIV) with hydrogen peroxide in boiling methanolic sodium hydroxide (compare Weitz *et al.*, *loc. cit.*). The resulting acid had m. p. 316°, and did not depress the m. p. of the acid obtained by oxidising the hydrocarbon with the Milas reagent, or that obtained by another route by Stephenson (*loc. cit.*), who gives m. p. 311—313°. For characterisation, the *methyl* ester of (XV) was prepared by the Fischer–Speier method. It formed almost colourless leaflets (from ethanol), m. p. 144—145° (Found : C, 77·3; H, 5·1. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%).

3 : 4-*Benzpyrene* (XVI).—The oxidation of this hydrocarbon with the Milas reagent proceeded as with pyrene. Chromatography on alumina of the benzene extract after concentration (a large volume of benzene was required) gave a red zone. The column was cut and this was eluted with chloroform. Repeated chromatography from benzene of the concentrated eluate resulted in partial separation into a lower (yellow) band and an upper (red) band. These were cut, eluted with chloroform, and concentrated. The residue from the yellow band gave a cherry-red solution in concentrated sulphuric acid, whereas that from the red band gave an olive-brown solution. These colours are consistent with the view that the yellow quinone is the 5 : 10-quinone and the red quinone the 5 : 8-quinone obtained by Vollmann *et al.* (*loc. cit.*) by chromic acid oxidation of 3 : 4-benzpyrene (XVI).

Some of the fractions from the chromatogram gave a deep violet colour with sulphuric acid and reacted with *o*-phenylenediamine in acetic acid to give a yellow precipitate, indicating an *o*-quinone. For comparison, the dihydroxydihydro-3 : 4-benzpyrene of Cook and Schoental (*loc. cit.*) was oxidised with chromic acid and the resulting *quinone*, probably the 6 : 7-quinone, crystallised from glacial acetic acid. It formed orange-red needles, m. p. 240° (decomp.), and gave the expected deep-violet solution in concentrated sulphuric acid (Found : C, 85·0; H, 3·6. $C_{20}H_{10}O_2$ requires C, 85·1; H, 3·55%). The *quinoxaline*, prepared by treatment with *o*-phenylenediamine in acetic acid, formed small yellow needles, m. p. 318° (decomp.), not depressed by admixture with the precipitate similarly formed from fractions of the chromatogram (Found : C, 87·8; H, 4·2; N, 7·8. $C_{26}H_{14}N_2$ requires C, 88·1; H, 4·0; N, 7·9%).

We thank the British Empire Cancer Campaign for a grant which has enabled one of us (R. S.) to take part in this work. We are also much indebted to Mr. J. Robertson for the gift of a specimen of *O*-tetra-acetyl*allo*mucic acid. Microanalyses were by Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW.

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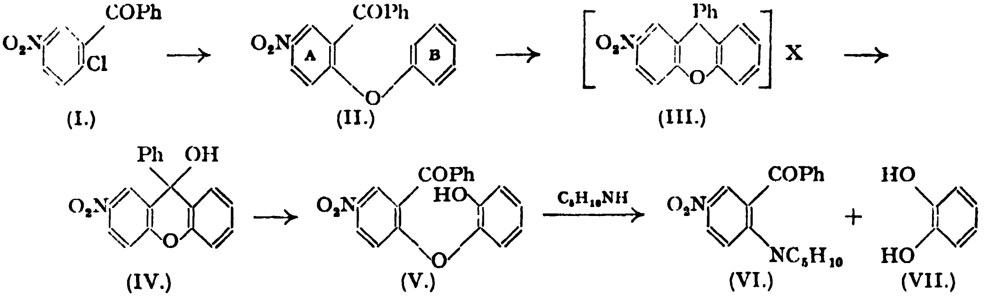
13. ortho-*Hydroxylation of Phenols. A New Case of the Smiles Rearrangement.*

By J. D. Loudon, J. R. Robertson, J. N. Watson, and (in part) (Miss) S. D. Aiton.

The potassium salts of various phenols condense with 2-chloro-5-nitrobenzophenone to form 5-*nitro*-2-*aryloxybenzophenones* which with concentrated sulphuric acid afford solutions of the corresponding 9-phenylxanthylium sulphates. These solutions yield (*a*) derivatives of 9-phenylxanth-hydrol when treated with water, or (*b*) 5-*nitro*-2-o-*hydroxyaryloxybenzophenones*, *e.g.*, (V), when treated with acetic acid and hydrogen peroxide. Compounds of type (V) react with piperidine to give catechol derivatives and 5-*nitro*-2-*piperidinobenzophenone*, form unstable, covalent sodium derivatives, and in particular cases rearrange in alkaline solution, the nitrobenzophenone residue migrating to the second oxygen atom of the catechol system, *e.g.*, (X) ⟶ (XI).

The following investigation was undertaken to test the practicability of the reaction scheme illustrated by (I)—(VII) and to define the respects requiring particular study in order to achieve a general development. Condensation between 2-chloro-5-nitrobenzophenone (I) and the potassium salts of various phenols afforded the aryl *ethers*, *e.g.*, (II), in satisfactory yields and, in most cases, these were converted smoothly into 9-phenylxanthylium salts by dissolution in cold concentrated sulphuric acid. The corresponding *xanth-hydrols*, *e.g.*, (IV), were obtained by pouring the solutions into water. This cyclisation process is analogous to that already described for the formation of thioxanthen derivatives (Loudon *et al.*, *J.*, 1941, 747) and, since it depends on nucleophilic reactivity in ring B [cf. (II)], was less readily accomplished in cases where this ring was nitrated.

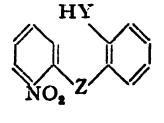


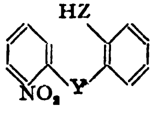
Quint and Dilthey (*Ber.*, 1931, **64**, 2082) have shown that 9-phenylxanthylium perchlorate is oxidised by hydrogen peroxide in acetic acid to 2-*o*-hydroxyphenoxybenzophenone (V; H for (NO_2)). Similar oxidation of *perchlorates* derived from our 2-nitro-9-phenylxanth-hydrols gave mainly neutral products, presumably *peroxides* of the type encountered by Dilthey (*loc. cit.*). In a number of cases, however, the required catechol derivatives, *e.g.*, (V), were very readily obtained by oxidising the xanth-hydrol in sulphuric–acetic acid, and the process gave excellent results with 9-phenylxanth-hydrol itself. Consequently, in these cases a simple and almost quantitative conversion of the phenol derivatives (II; ring B = phenyl, or *o*-, *m*-, or *p*-tolyl) into the catechol derivatives, *e.g.*, (V), was achieved by dissolving the former in concentrated sulphuric acid, diluting the solution with acetic acid and adding hydrogen peroxide. That the pyrylium ring opens in the sense shown was confirmed by the identity of the methylation product of (V) with the condensation product obtained from (I) and guaiacol.

The final stage of the reaction scheme, *viz.*, liberation of the catechol from its aryl ether, was not examined extensively. The scission of *o*- or *p*-nitrated diaryl ethers by means of piperidine is well known (Le Fèvre, Saunders, and Turner, *J.*, 1927, 1168; Groves, Turner, and Sharp, *J.*, 1929, 512) and we have limited our present inquiry to a few test cases using this reagent. Catechol, 3 : 4-dihydroxytoluene, and 4-hydroxy-3-methoxytoluene were isolated from (V), (XI), and (XI*a*), respectively, and in each case 5-*nitro*-2-*piperidinobenzophenone* was also produced.

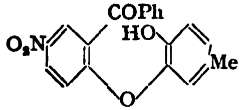
Since it is part of our project to study the extension of the process through renewed cyclisation at the catechol stage (V), with or without alkylation of the free phenolic group, it became necessary to examine the behaviour of the catechol derivatives particularly towards alkaline reagents. Smiles and his collaborators have shown (for summary and references, cf. *Ann. Reports*, 1939, **36**, 197) that the different donor-capacities in dissimilar atoms Y and Z constitute an important factor in the rearrangement of (VIII) to (IX). Different donor-capacities will also exist where Y and Z represent atoms of the same element dissimilarly situated in the molecule. This condition and other essential features for rearrangement are present in the isomers (X) and (XI). Experiment indeed showed that when (X) was dissolved in aqueous alkali it was almost completely rearranged to the compound which had already been obtained by hydroxylating the *p*-tolyl ether (II; ring B = *p*-tolyl) and which, accordingly, has the formula (XI). For this reason also methylation of either (X) or (XI) by methyl sulphate in alkali afforded the same *methyl ether* (XI*a*), which was identified by scission with piperidine to

(VIII.)

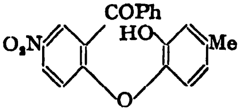




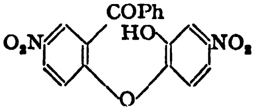
(IX.)



(X.)
(X*a*; MeO for HO.)



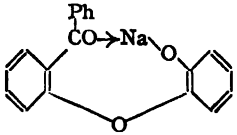
(XI.)
(XI*a*; MeO for HO.)



(XII.)

4-hydroxy-3-methoxytoluene as already mentioned. On the other hand, methylation without rearrangement was effected by means of diazomethane, which gave (X*a*) and (XI*a*) from (X) and (XI), respectively, the *ether* (X*a*) being identified by its formation from (I) and 3-hydroxy-4-methoxytoluene. There was also evidence of rearrangement in the case of the *nitrocatechol* derivative (XII) which was prepared from *p*-nitrophenol *via* 2 : 7-*dinitro*-9-*phenylxanth-hydrol*. The compound appeared to be isomerised by dissolution in alkali and the same change, displayed as a double melting point, occurred on heating the substance in soft-glass but not in hard-glass tubes. Unfortunately, synthesis of the compound, which would be expected as rearrangement product of (XII), was prevented by the difficulty of effecting the cyclisation step (II) ⟶ (III) where ring B contains a *m*-nitro-substituent. Nitration of (I) yielded 2-*chloro*-3′ : 5-*dinitrobenzophenone* from which by condensation with *m*- and *p*-cresol, followed by hydroxylation, there were prepared respectively 3′ : 5-*dinitro*-2-(2-*hydroxy*-5-*methylphenoxy*)- and 3′ : 5-*dinitro*-2-(2-*hydroxy*-4-*methylphenoxy*)-*benzophenone*. In alkaline solution the former of these compounds was isomerised to the latter, corresponding with the rearrangement of (X) to (XI). It is probable that in the cases examined rearrangement is not complete but reaches an equilibrium point. This is suggested by the fact that the products of rearrangement, like the synthetic samples when recovered from solution in alkali, melt lower and less sharply than the pure compounds.

In the course of these experiments in alkaline media it was noted that the sodium and potassium salts of the catechol derivatives of type (V) were only sparingly soluble in aqueous alkali. Further examination showed that in these compounds the metal is present in the covalent condition. The compounds were obtained as yellow crystalline solids of low melting points; they were sparingly soluble in cold water and were hydrolysed to the metal-free compounds by warm water; they dissolved readily in warm benzene or chloroform, losing water and giving orange-coloured solutions from which less coloured, lower hydrated forms separated on cooling. Their general instability made it difficult to secure consistent and reliable analytical data. Quint and Dilthey (*loc. cit.*) describe a yellow sodium salt of 2-(*o*-hydroxyphenoxy)benzophenone and re-examination of this compound showed that here too the metal is covalently bound. Since corresponding salts of 2-hydroxydiphenyl ether are of the normal type, the carbonyl group of the present compounds appears to take part in the covalent linking of the metal. By analogy with the covalent alkali derivatives of salicylideneacetophenone and related compounds investigated by Smiles and his colleagues (cf. Dvorkovitz and Smiles, *J.*, 1938, 2022), this suggests a structure such as (XIII) containing a strainless 9-membered ring. It is noteworthy, however, that these authors were unable to find evidence of stable ring structures of this type containing more than eight members.



(XIII.)

EXPERIMENTAL.

2-*Chloro*-3′ : 5-*dinitrobenzophenone*.—Solutions of 2-chloro-5-nitrobenzophenone (4·4 g.) (Fries, *Annalen*, 1927, **454**, 287) and potassium nitrate (1·7 g.) in the requisite quantity of concentrated sulphuric acid were mixed and, after 12 hours at room temperature, the mixture was poured into ice-water. The *product* formed colourless plates, m. p. 177°, from acetic acid (Found : C, 51·0; H, 2·3; N, 9·3. $C_{18}H_7O_5N_2Cl$ requires C, 50·9; H, 2·3; N, 9·1%).

For the preparation of the aryloxybenzophenones the chloronitrobenzophenone (1 mol.) was added to a fused mixture of the appropriate phenol (1—2 mols.) and its potassium salt (1·2 mols.). Gentle heating initiated an exothermic reaction which was allowed to complete itself and after further brief heating (in all 15—20 minutes) the mass was cooled and treated with a dilute solution of sodium hydroxide. The solidified product was crystallised from acetic acid, diluted if necessary. In this way the tabulated compounds were prepared from 2-chloro-5-nitrobenzophenone or from 2-chloro-3′ : 5-dinitrobenzophenone.

Aryl group.	M. p.	Formula.	Found, %. C.	Found, %. H.	Required, %. C.	Required, %. H.
5-*Nitro*-2-*aryloxybenzophenones.*						
Phenyl	150°	$C_{19}H_{13}O_4N$	71·8	4·3	71·5	4·1
o-Tolyl	121—122	$C_{20}H_{15}O_4N$	72·2	4·3	72·1	4·5
m-Tolyl	106	$C_{20}H_{15}O_4N$	72·0	4·6	72·1	4·5
p-Tolyl	129	$C_{20}H_{15}O_4N$	72·1	4·3	72·1	4·5
o-Methoxyphenyl	132	$C_{20}H_{15}O_4N$	72·0	4·5	72·1	4·5
m-Chlorophenyl	117	$C_{19}H_{12}O_4NCl$	64·9	3·5	64·5	3·4
p-Chlorophenyl	118	$C_{19}H_{12}O_4NCl$	64·8	3·3	64·5	3·4
m-Nitrophenyl	116—117	$C_{19}H_{12}O_6N_2$	62·8	3·5	62·6	3·3
p-Nitrophenyl	106	$C_{19}H_{12}O_6N_2$	62·6	3·2	62·6	3·3
2-Methoxy-5-methylphenyl	120	$C_{21}H_{17}O_5N$	69·7	4·8	69·4	4·7
β-Naphthyl	137—138	$C_{23}H_{15}O_4N$	74·75	4·2	74·8	4·1
3′ : 5-*Dinitro*-2-*aryloxybenzophenones.*						
Phenyl	73	$C_{19}H_{12}O_6N_2$	62·3	3·7	62·6	3·3
m-Tolyl	123	$C_{20}H_{14}O_6N_2$	63·8	3·6	63·5	3·7
p-Tolyl	184	$C_{20}H_{14}O_6N_2$	63·5	3·8	63·5	3·7

2-*Nitro*-9-*phenylxanth-hydrol* (IV), m. p. 184° [from benzene-petroleum (b. p. 60—80°)] (Found : C, 71·55; H, 4·1. $C_{19}H_{13}O_4N$ requires C, 71·5; H, 4·1%), was prepared by dissolving 5-nitro-2-phenoxybenzophenone in cold concentrated sulphuric acid and, after an hour at room temperature, pouring the red solution into ice-water. The *xanthylium perchlorate*, m. p. 211° (Found : C, 56·7; H, 3·4. $C_{19}H_{12}O_3N{\cdot}ClO_4$ requires C, 56·7; H, 3·0%), was obtained as orange-red crystals when perchloric acid (0·11 g.) was added to a warm solution of the xanth-hydrol (0·2 g.) in acetic acid (5·5 c.c.).

In similar fashion the following were prepared from the appropriate 5-nitro-2-aryloxybenzophenone : 2-*nitro*-9-*phenyl*-6-*methylxanth-hydrol*, m. p. 186° (Found : C, 72·2; H, 4·5. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%); 2-*nitro*-9-*phenyl*-7-*methylxanth-hydrol*, m. p. 163° (Found : C, 72·1; H, 4·7. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%) [the derived *perchlorate* had m. p. 260° (decomp.) (Found : C, 57·5; H, 3·5. $C_{20}H_{14}O_3N{\cdot}ClO_4$ requires C, 57·7; H, 3·6%)]; 2-*nitro*-9-*phenyl*-7 : 8-*benzxanth-hydrol*, m. p. 240° (Found : C, 74·6; H, 4·3. $C_{23}H_{15}O_4N$ requires C, 74·8; H, 4·1%); and 2 : 7-*dinitro*-9-*phenylxanth-hydrol*, m. p. 194—195° (Found : C, 62·8; H, 3·2. $C_{19}H_{12}O_6N_2$ requires C, 62·6; H, 3·3%). Cyclisation in the last case was completed by heating a solution of the ketone (2 g.) in concentrated acid (25 c.c.) at 120—130° for 20 minutes, but even these conditions failed to achieve a satisfactory cyclisation with 5-nitro-2-*m*-nitrophenoxybenzophenone which was recovered largely unchanged although the red colour of the solution indicated partial formation of the xanthylium salt.

2-o-*Hydroxyphenoxybenzophenone*.—A solution of 9-phenylxanth-hydrol (1 g.) in concentrated sulphuric acid (1 c.c.) was diluted with acetic acid (11 c.c.), and hydrogen peroxide was added dropwise and with shaking. The initial yellow colour of the solution rapidly changed to orange-red which gradually faded to a pale yellow (*ca.* 1 hour). At this stage the mixture, in which some colourless flaky crystals appeared, was poured into water. The partly solid gum solidified when rubbed with ethanol, yielding 2-*o*-hydroxyphenoxybenzophenone (0·95 g.), m. p. 103—104°, from ethanol (Quint and Dilthey, *loc. cit.*, give m. p. 104°).

Sodium derivative. The above compound dissolved in warm dilute sodium hydroxide to form a yellow solution from which, on cooling, the sodium salt separated as beautiful yellow leaflets (Found: C, 53·8; H, 5·8. Calc. for $C_{19}H_{13}O_3Na,6H_2O$: C, 54·3; H, 5·95%). When slowly heated these sintered at 80—90° and melted quite sharply at 135—136°; when suddenly exposed to a temperature of 100—110° they rapidly liquefied, re-solidified, and again melted at 135°. They appeared to be insoluble in cold water but when shaken with warm water gave first a turbid and then a clear solution from which, on cooling, needles of the parent compound, m. p. and mixed m. p. 102—104°, were deposited. On the other hand, when heated with benzene they dissolved, water being liberated, and the hot filtered solution deposited the *trihydrate* as a mass of fine colourless needles which gave a clear yellow melt at 135—136° and did not melt when plunged into a bath at 110° (Found : C, 62·9; H, 4·8. $C_{19}H_{13}O_3Na,3H_2O$ requires C, 62·3; H, 5·2%).

5-*Nitro*-2-o-*hydroxyphenoxybenzophenone* (V).—(i) A suspension of 5-nitro-9-phenylxanthylium perchlorate (1 g.) in acetic acid (10 c.c.) was treated with 30% hydrogen peroxide (2 c.c.). The colour of the salt was gradually discharged and after 12 hours at room temperature the colourless crystalline solid (*A*) was collected, and the filtrate, on dilution with water gave a flocculent precipitate. The latter, which was completely soluble in dilute sodium hydroxide, afforded the compound (V) (cf. below), and was converted by reaction with methyl sulphate in alkaline solution into 5-nitro-2-*o*-methoxyphenoxybenzophenone, m. p. and mixed m. p. 130—132°. The crystalline solid (*A*), which was the main product of the reaction, was insoluble in cold dilute alkali, liberated iodine from a solution of potassium iodide and was probably a *peroxide* derived from the xanth-hydrol (cf. Quint and Dilthey, *loc. cit.*); it had m. p. 180° (decomp.) (from acetic acid) (Found: C, 68·1; H, 4·2. $C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9%). (ii) 5-Nitro-2-phenoxybenzophenone (2·6 g.) was dissolved in cold concentrated sulphuric acid (4·2 c.c.) and, after 30 minutes, acetic acid (26 c.c.) was added. With vigorous stirring but without external cooling, hydrogen peroxide (6 c.c.) was then added fairly rapidly (5 minutes) and the whole was kept at room temperature for 3 hours. The mixture was then poured into water, giving the required *product* (V) in almost quantitative yield. It formed faintly yellow needles, m. p. 159°, from ethanol (Found: C, 68·2; H, 4·1. $C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9%).

5-*Nitro*-2-(2-*hydroxy*-4-*methylphenoxy*)*benzophenone* (XI) was similarly obtained (i) from 2-nitro-7-methylxanthylium perchlorate which also yielded mainly a *peroxide*, m. p. 210° (decomp.) (Found: C, 69·0; H, 4·3. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and (ii) from 5-nitro-2-*p*-tolyloxybenzophenone. It formed pale yellow needles, m. p. 150°, from ethanol (Found: C, 68·8; H, 4·2. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and yielded 5-*nitro*-2-(2-*methoxy*-4-*methylphenoxy*)*benzophenone* (XI*a*) as colourless needles, m. p. 100—101° (from methanol) (Found: C, 69·8; H, 4·8. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7%), when methylated either with diazomethane in ether or with methyl sulphate in aqueous sodium hydroxide. By acidifying solutions of (XI) in aqueous or ethanolic potassium hydroxide, which had been kept at room temperature for periods up to 5 days, the compound was recovered mainly unchanged, although the m. p. and mixed m. p. 145—148° was invariably lower even after crystallisation.

5-*Nitro*-2-(2-*hydroxy*-5-*methylphenoxy*)*benzophenone* (X), m. p. 158° (Found: C, 68·9; H, 4·1. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), and 5-*nitro*-2-(2-*hydroxy*-6-*methylphenoxy*)*benzophenone*, m. p. 127—128° (Found: C, 68·7; H, 4·4%), were similarly prepared from the appropriate 5-nitro-2-aryloxybenzophenones. When solutions of (X) in acetone and diazomethane in ether were mixed and kept at room temperature for 2 days, concentration of the resulting solution afforded 5-nitro-2-(2-methoxy-5-methylphenoxy)benzophenone (X*a*), m. p. and mixed m. p. 120° (from ethanol), whereas methylation of (X) with methyl sulphate in dilute sodium hydroxide gave (XI*a*), m. p. and mixed m. p. 100—101°. Acidification of a solution of (X) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 24 hours, gave a phenolic product, m. p. 145—147° (from ethanol), unchanged by admixture with (XI) but depressed to m. p. 130—134° by admixture with (X).

5-*Nitro*-2-(4-*nitro*-2-*hydroxyphenoxy*)*benzophenone*.—A solution of 2 : 7-dinitro-9-phenylxanth-hydrol (0·7 g.) in concentrated sulphuric acid (3 c.c.) was treated successively with acetic acid (6 c.c.) and 30% hydrogen peroxide (1·5 c.c.) and the whole was kept at 40° for 1 hour. After addition to water the solid was collected and extracted with 90% ethanol, leaving an unidentified insoluble residue, m..p. 265° (Found: C, 63·5; H, 3·0%). On cooling (charcoal), the solution deposited colourless needles, m. p. 168—170° when determined in quartz or Jena-glass capillary tubes, but sintering at 166° and melting at *ca.* 200° in tubes of soft glass (Found: C, 60·2; H, 3·3. $C_{19}H_{12}O_7N_2$ requires C, 60·0; H, 3·2%). The *compound* was readily soluble in dilute alkali, acidification yielding a solid, which formed long colourless needles, m. p. 208—210° (quartz), from ethanol (Found: C, 60·1; H, 3·1%). The change in m. p. is probably due to rearrangement to 5-nitro-2-(5-nitro-2-hydroxyphenoxy)benzophenone but attempts to confirm this by methylation with diazomethane gave in each case a gummy product which resisted crystallisation.

3′ : 5-*Dinitro*-2-(2-*hydroxy*-4-*methylphenoxy*)*benzophenone*, m. p. 203° (from acetic acid) (Found: C, 61·0; H, 3·5. $C_{20}H_{14}O_7N_2$ requires C, 60·9; H, 3·35%), and 3′ : 5-*dinitro*-2-(2-*hydroxy*-5-*methylphenoxy*)*benzophenone*, m. p. 162° (from methanol) (Found: C, 61·1; H, 3·5%), were prepared in the usual way from 5-nitro-2-*p*- and -*m*-tolyloxybenzophenone respectively (0·5 g.) in concentrated sulphuric acid (2 c.c.) and acetic acid (5 c.c.) by warming with 30% hydrogen peroxide at 40°. The latter product was converted into the former, m. p. and mixed m. p. 201—202°, by dissolution in, and recovery from, dilute potassium hydroxide.

Scissions with Piperidine.—(i) A solution of 5-nitro-2-*o*-hydroxyphenoxybenzophenone (V) in piperidine was heated under reflux for 1 hour. After cooling and addition of benzene, the resulting solution was washed with dilute sulphuric acid and then with dilute sodium hydroxide. Acidification of the alkaline extract and recovery in ether afforded catechol, m. p. and mixed m. p. 103—104°, after distillation (diacetate, m. p. and mixed m. p. 63°). Concentration of the dried benzene solution gave 5-*nitro*-2-*piperidinobenzophenone* (VI), m. p. 100° (from ethanol), identical with a specimen prepared from (I) and piperidine (Found: N, 9·2. $C_{18}H_{18}O_3N_2$ requires N, 9·0%).

(ii) 5-Nitro-2-(2-hydroxy-4-methylphenoxy)benzophenone (XI) when similarly treated with piperidine afforded (VI) and 3 : 4-dihydroxytoluene. The latter was obtained as a red oil after acidication of the alkaline extract and recovery from ether; it afforded a solid distillate, m. p. 64°, and with bromine in acetic acid gave the tribromo-derivative, m. p. 158—160° (Ono and Imoto, *Bull. Soc. Chem. Japan*, 1936, **11**, 127, give m. p. 158°).

(iii) 5-Nitro-2-(2-methoxy-4-methylphenoxy)benzophenone (XI*a*) likewise yielded (VI) and 4-hydroxy-3-methoxytoluene. The latter was obtained as a pale yellow oil of characteristic odour and giving with ferric chloride in ethanol the blue and green colour reactions mentioned by de Vries (*Rec. Trav. chim.*, 1909, **28**, 276); with picric acid in ethanol it afforded orange-red needles of the picrate, m. p. 98—99° (from aqueous ethanol) (Beilstein records m. p.s 96°, 96·8°, and 112°).

Micro-analyses were carried out by Mr. J. M. L. Cameron.

THE UNIVERSITY, GLASGOW.

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14. *The Role of* E_g^+ *Vibrations in the* 2600-A. *Benzene Band System.*

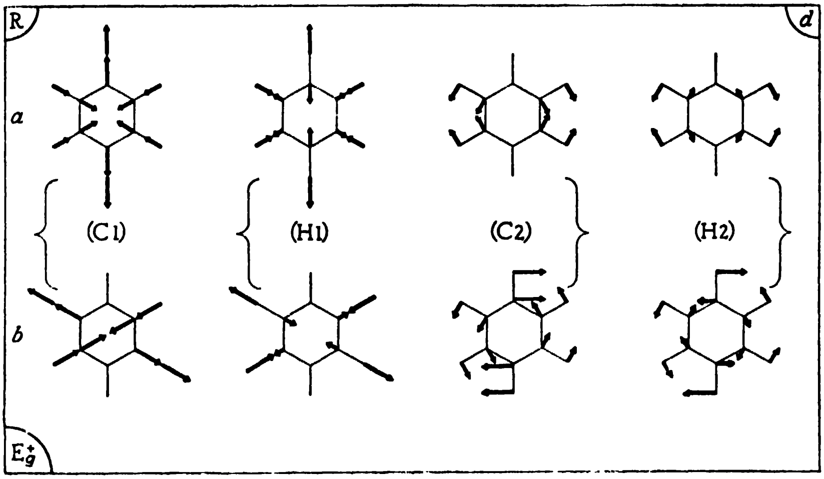
By D. P. Craig.

The observation by Garforth and Ingold (*J.*, 1948, 417) that the two E_g^+(C) vibrations differ strongly in their power to perturb the forbidden $A_{1g} - B_{2u}$ transition in benzene receives an explanation in terms of an assumed mechanism for the perturbation of electronic states by atomic vibrations. The mechanism, which in spite of a certain reasonableness must at present be treated as heuristic, is that each C atom in the benzene ring acts towards non-neighbours as a small positive charge but is completely screened from its neighbours. Electronic wave functions are approximated in terms of structures, and of these the polar ones here play the central part. The energy matrix components are changed in the course of vibrations by electrostatic action between the small charges already mentioned and the unit charges of polar structures. The 606-cm.$^{-1}$ vibration can then be calculated to be more effective, by a factor greater than 100 times, than the 1596-cm.$^{-1}$ vibration in causing the appearance of the forbidden transition. This agrees with the experimental finding.

Herzberg and Teller (*Z. physikal. Chem.*, 1933, *B*, **21**, 410) established the principles, so far as the demands of symmetry are concerned, which govern the disturbances caused to electronic states by atomic vibrations in polyatomic molecules. A spectral transition forbidden by electronic selection rules is made allowed if the symmetry properties of the atomic vibrations change during the transition by a component $\Gamma_{\text{vib.}}$ such that

$$\Gamma_{\text{Gd}} \times \Gamma_{\text{Exc.}} \times \Gamma_{\text{vib.}} \subset \Gamma_x, \Gamma_y, \text{ or } \Gamma_z$$

where Γ_{Gd} and $\Gamma_{\text{Exc.}}$ are the representations to which the ground and the excited electronic wave functions belong and Γ_x, for example, that of the x vector. However, Garforth and Ingold (*J.*, 1948, 417) showed that, of the four E_g^+ vibrations of benzene capable in principle of making the 2600 A. transition appear, only two actually do so and in these two the motions of the C skeleton are geometrically similar. The figure is part of a block of illustrations used by Bailey, Ingold, Poole, and Wilson (*J.*, 1946, 222) to show the vibration forms of benzene and it is reproduced here with their permission. It depicts a set of basic E_g^+ motions from which, by linear combination, all possible E_g^+ motions of benzene can be set up. Garforth and Ingold (*loc. cit.*) find that the two vibrations with a large component of either the C1 or the H1 motion—in which, that is, the C hexagon is distorted principally by angle bending and not by bond stretching—are effective, whereas those with a large component of C2 or H2 are ineffective. The latter equally with the former satisfy the symmetry demands but fail to appear on account of some more subtle detail of the atomic motions. To understand how this can happen a mechanism has to be assumed by which the electronic energy comes to depend on the nuclear motion, and this should make it plain how the observed differences come about. A very simple



E_g^+ *Vibration forms of benzene.*

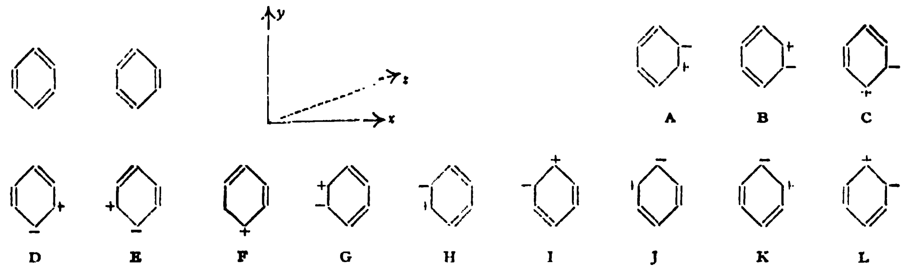
mechanism is applied in this paper to study those two vibrational motions, compounded from C1 and C2, in which the carbon atoms have large amplitudes, and it is found that one of these could be very much more effective than the other in this phenomenon. The effective one is the predominantly bending motion, as required by experiment.

The intense absorption band of benzene at 1700 A. records an $\mathbf{A}_{1g}$ — $\mathbf{E}_u^-$ transition, and any forbidden transition which appears at longer wave-lengths does so mainly by borrowing intensity from this strong band. We concentrate therefore on finding to what extent E_g^+ vibrations cause mixing of the final $\mathbf{B}_{2u}$ state of the forbidden transition with the final $\mathbf{E}_u^-$ state of the allowed one. The coefficient for this mixing is, in perturbation theory,

$$\frac{\int\psi(\mathbf{B}_{2u})(EH'^{+}_{g})\psi(\mathbf{E}_u^-)\mathrm{d}\tau}{E(\mathbf{B}_{2u})-E(\mathbf{E}_u^-)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which ψ and E respectively denote unperturbed wave functions and energies, and $H'(E_g^+)$ is the perturbing potential of a hexagon distorted in an E_g^+ vibration. The intensity of the transition ending at the $\mathbf{B}_{2u}$ state will bear the same ratio to the allowed $\mathbf{A}_{1g}$ — $\mathbf{E}_u^-$ intensity as the square of the expression (1) bears to unity; hence to compare the perturbing powers of the two E_g^+ vibrations (*i.e.*, the two C vibrations) we have to compare the squares of (1) evaluated for them.

We may write approximate forms for $\psi(\mathbf{E}_u^-)$ and $\psi(\mathbf{B}_{2u})$ in terms of the following structures :



Two $\mathbf{E}_u^-$ wave functions may be made up from these and both involve only the polar structures A to L. Of the two the following one alone may be the final state for intense transitions :

$$\psi(\mathbf{E}_u^-) = (1/\sqrt{24})(2\mathrm{A} - 2\mathrm{B} + \mathrm{C} - \mathrm{D} - \mathrm{E} + \mathrm{F} - 2\mathrm{G} + 2\mathrm{H} - \mathrm{I} + \mathrm{J} + \mathrm{K} - \mathrm{L}) \quad . \quad (2)$$

A degenerate partner to (2), chosen orthogonal to it, is inactive in the mechanism we consider and hence may be neglected. The $\mathbf{B}_{2u}$ state which, to appear in the spectrum, has to become mixed with $\psi(\mathbf{E}_u^-)$ has non-polar as well as polar components. We follow in detail only the polar part, $\psi(\mathbf{B}_{2u})$. The contribution by the non-polar part is in the same sense and proportional, but is smaller because it appears multiplied by the overlap integral between neighbouring atomic orbitals. We therefore take

$$\psi(\mathbf{B}_{2u}) = (1/\sqrt{12})(\mathrm{A} + \mathrm{B} - \mathrm{C} - \mathrm{D} + \mathrm{E} + \mathrm{F} - \mathrm{G} - \mathrm{H} + \mathrm{I} + \mathrm{J} - \mathrm{K} - \mathrm{L}) \quad . \quad . \quad (3)$$

If H be the Hamiltonian for the undistorted hexagonal shape it follows from the symmetry of the problem that

$$\int\psi(\mathbf{E}_u^-)H\psi(\mathbf{B}_{2u})\mathrm{d}\tau = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

A distortion from hexagonal shape replaces H in (4) by $H + H'$, H' being a perturbing potential having the symmetry of the distortion. When H' transforms like E_g^+ the matrix component analogous to that in (4) has a part which transforms like A_{1g} and is not therefore necessarily zero. Small terms being neglected, the totally symmetrical part is

$$\begin{aligned}\int\psi(\mathbf{E}_u^-)H'\psi(\mathbf{B}_{2u})\mathrm{d}\tau &= (1/12\sqrt{2})\{2(\mathrm{A}H'\mathrm{A}) - 2(\mathrm{B}H'\mathrm{B}) - (\mathrm{C}H'\mathrm{C}) + (\mathrm{D}H'\mathrm{D}) \,..\, \mathrm{etc}\} \\ &= (1/2\sqrt{2})\{(\mathrm{A}H'\mathrm{A}) - (\mathrm{B}H'\mathrm{B})\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)\end{aligned}$$

where $(\mathrm{A}H'\mathrm{A}) = \int \mathrm{A}H'\mathrm{A}\mathrm{d}\tau$

the second line following from the first because H' transforms like E_g^+. The value of this expression, put in (1), determines the intensity of the forbidden band system. Evidently its value depends on the development of energy differences under the perturbing vibration between structures in pairs like A and B which have opposite charge displacements. We therefore have to investigate the right-hand side of (5) by seeing how the energies of oppositely charged structures are split by atomic motions of specified types.

The energies of these polar structures change during the course of vibrations because the internuclear distances change, and this alters the mutual energy of the charged atoms and the other nuclei. Since at distances greater than a bond length the field of an atom is dominantly electrostatic (the exchange terms being negligibly small) the energy changes we wish to study may be taken to arise from the electrostatic action between the unit positive and negative charges in the structure, and the field of the incompletely screened nuclear charge of the other atoms. Now screening is most complete in the directions of maximum electron density (*i.e.*, bond directions) so it is evident from the outset that a distinction must be made between neighbour and non-neighbour interactions, the former being smaller than the latter by virtue of the more complete screening along the line of the σ bonds. Accordingly we propose, as the simplest reasonable model, that any nucleus acts toward a non-neighbour as a small positive charge qe, but is completely shielded from its immediate neighbours by the bonding electrons. Interest throughout centres on energy differences developed between oppositely charged structures, so that no attention need be paid to the interaction between the charged atoms which changes by the same amount in the two structures. We thus suppose that in any structure there are on the non-charged atoms small residual charges qe, and that energy changes in distorted molecules are a consequence of interactions between the two charged atoms and these small charges on non-neighbours.

We now proceed with the calculation of the perturbation energies. Since the displacements are small compared with a bond length we use the differential expression for change in electrostatic energy:

$$\delta E = (qe^2/r^2)\delta r \equiv \mathcal{A}(r_b^2/r^2)\delta r, \text{ where } \mathcal{A} = qe^2/r_b^2 \text{ and } r_b = 1{\cdot}40 \text{ A.}$$

Since $\psi(\mathbf{B}_{2u})$ is symmetric, but $\psi(\mathbf{E}_u^-)$ antisymmetric, to rotation about the x axis, antisymmetry in the vibrational motion will be necessary to cause mixing. Only the lower forms of C1 and C2 need therefore be studied. We suppose the atoms in the lower form of C1 to be displaced a distance $\delta r/2$, and in the lower form of C2 the clockwise displacements are δr and the anticlockwise ones $\delta r/2$. This choice is merely a convenient one for the next step, and the composite motions have later to be normalised to unit kinetic energy. The distortion energies are:

Structure A, distorted according to C1 (lower form)

$$\Sigma\delta E = -2\mathcal{A}(1/4 + \sqrt{3}/12)\delta r$$

Structure A, distorted according to C2 (lower form)

$$\Sigma\delta E = \tfrac{1}{2}\mathcal{A}\delta r$$

Substituting in (5), we have

$$\left.\begin{aligned} \int \psi(\mathbf{B}_{2u})H(\mathrm{C1})\psi(\mathbf{E}_u^-)d\tau &= -\sqrt{2}(1/4 + \sqrt{3}/12)\,\mathcal{A}\delta r = -0{\cdot}558\,\mathcal{A}\delta r \\ \int \psi(\mathbf{B}_{2u})H(\mathrm{C2})\psi(\mathbf{E}_u^-)d\tau &= 1/2\sqrt{2}\mathcal{A}\delta r \qquad\qquad = 0{\cdot}354\,\mathcal{A}\delta r \end{aligned}\right\} \quad . \quad . \quad . \quad (6)$$

The actual molecular motions in E_g^+ vibrations are combinations of C1 and C2 in proportions determined by the force system opposing distortions of the equilibrium hexagon. To find these actual motions we proceed in the simplest way, by supposing the C–H groups concentrated in mass points and taking a valence-force field with C–C stretching and C–C–C planar bending force constants as found by Ingold and his collaborators (*J.*, 1948, 491). Referred to the lower forms of the illustrated motions, the actual motions after being normalised to equal kinetic energies are:

$$0{\cdot}90\mathrm{C1} - 0{\cdot}25\mathrm{C2}: \text{ calc. } 616 \text{ cm.}^{-1} \text{ (exptl. } 606 \text{ cm.}^{-1})$$

$$0{\cdot}44\mathrm{C1} + 0{\cdot}52\mathrm{C2}: \text{ calc. } 1657 \text{ cm.}^{-1} \text{ (exptl. } 1596 \text{ cm.}^{-1})$$

Using (6), we now find the matrix components for the mixing of $\mathbf{B}_{2u}$ and $\mathbf{E}_u^-$ states by these two vibrations.

$$606 \text{ cm.}^{-1}: \int \psi(\mathbf{B}_{2u})\{0{\cdot}90H(\mathrm{C1}) - 0{\cdot}25\,H(\mathrm{C2})\}\psi(\mathbf{E}_u^-)\,d\tau$$
$$= -0{\cdot}591\,\mathcal{A}\delta r$$

$$1596 \text{ cm.}^{-1}: \int \psi(\mathbf{B}_{2u})\{0{\cdot}44H(\mathrm{C1}) + 0{\cdot}52H(\mathrm{C2})\}\psi(\mathbf{E}_u^-)\,d\tau$$
$$= -0{\cdot}063\,\mathcal{A}\delta r$$

The relative effectiveness of the vibrations per unit excursion of the nuclei is the ratio of the squares of these quantities. Since the low-frequency motion has a larger amplitude than the high, the ratio of squares has to be increased in favour of the 606-cm.$^{-1}$ vibration by a factor (1596/606), making the final result:

$$\frac{\text{Intensity in } \mathbf{A_{1g}} - \mathbf{B_{2u}} \text{ due to 606 cm.}^{-1}}{\text{Intensity in } \mathbf{A_{1g}} - \mathbf{B_{2u}} \text{ due to 1596 cm.}^{-1}} = \frac{(-0{\cdot}591)^2}{(-0{\cdot}063)^2} \times \frac{1596}{606} = 230:1$$

We do not wish to insist on the numerical magnitude of the ratio, which is rather sensitive to the elastic constants chosen to determine the motions. However, in making the forbidden transition allowed, the 606-cm.$^{-1}$ vibration is certainly more effective, by a factor greater than 100 times, than the 1596 cm.$^{-1}$, and this agrees with the observation by Garforth and Ingold (*loc. cit.*) that the latter vibration is actually inactive, or very weak, in the spectrum.

An estimate of the intensity $\mathbf{A_{1g}} - \mathbf{B_{2u}}$. With one further assumption it is possible to form an estimate of the stolen intensity in the 2600-A. band system. Such a calculation, compared with experiment, gives a partial check of the mechanism of perturbation that has been assumed. The quantity required for evaluating (1) is qe, from which $\mathcal{A}$ can be found. For this we use Slater's rules for atomic screening constants, and suppose that at remote points a nucleus has the field expected outside the atomic configuration $(1s)^2(2s, 2p)^4$. This gives $qe = -0{\cdot}6$ electron. The root mean square excursion of a nucleus in the 606-cm.$^{-1}$ vibration is 0·064 A., and the coefficient of $\psi(\mathbf{B_{2u}})$ in the full wave function for the $\mathbf{B_{2u}}$ state (including non-polar as well as polar structures) is about 0·5. The perturbation matrix component is

$$\int \psi(\mathbf{B_{2u}}) H \psi(\mathbf{E_u^-}) d\tau = 0{\cdot}09\ e\text{V}.$$

and this, through (1), gives f (calc.) = 0·0014 as the calculated stolen intensity. The experimental value is f (exptl.) = 0·002. The close agreement is fortuitous. The important thing is the agreement in order of magnitude and the calculation is satisfactory to that extent.

I am very much indebted to Prof. C. K. Ingold, F.R.S., and to Dr. Edward Teller, for discussions on this subject. I also thank Prof. Ingold and his collaborators for permission to reproduce their diagram of vibration forms. The work described has been carried out during the tenure of a Turner and Newall Fellowship in the University of London.

Sir William Ramsay and Ralph Forster Laboratories,
University College, London.

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15. *Preparation of* L-*Threonine. Interconversion of the Four Stereoisomeric α-Amino-β-hydroxybutyric Acids.*

By D. F. Elliott.

Resolution of *trans*-DL-2-phenyl-5-methyl-Δ^2-oxazoline-4-carboxylic acid with brucine affords the L-form (I) of the acid as a crystalline brucine salt. The D-form (IV) remaining in the mother-liquors was also converted into (I) by a stepwise inversion process. Almost all of the racemic acid was thus transformed into the L-form. Hydrolysis of (I) gave pure L-threonine in 22% overall yield from hippuric acid. A cycle of asymmetric transformations has been worked out whereby any one of the four stereoisomers of α-amino-β-hydroxybutyric acid may be prepared from (I). The configurations of the two *allo*threonines have been determined by reference to L-threonine.

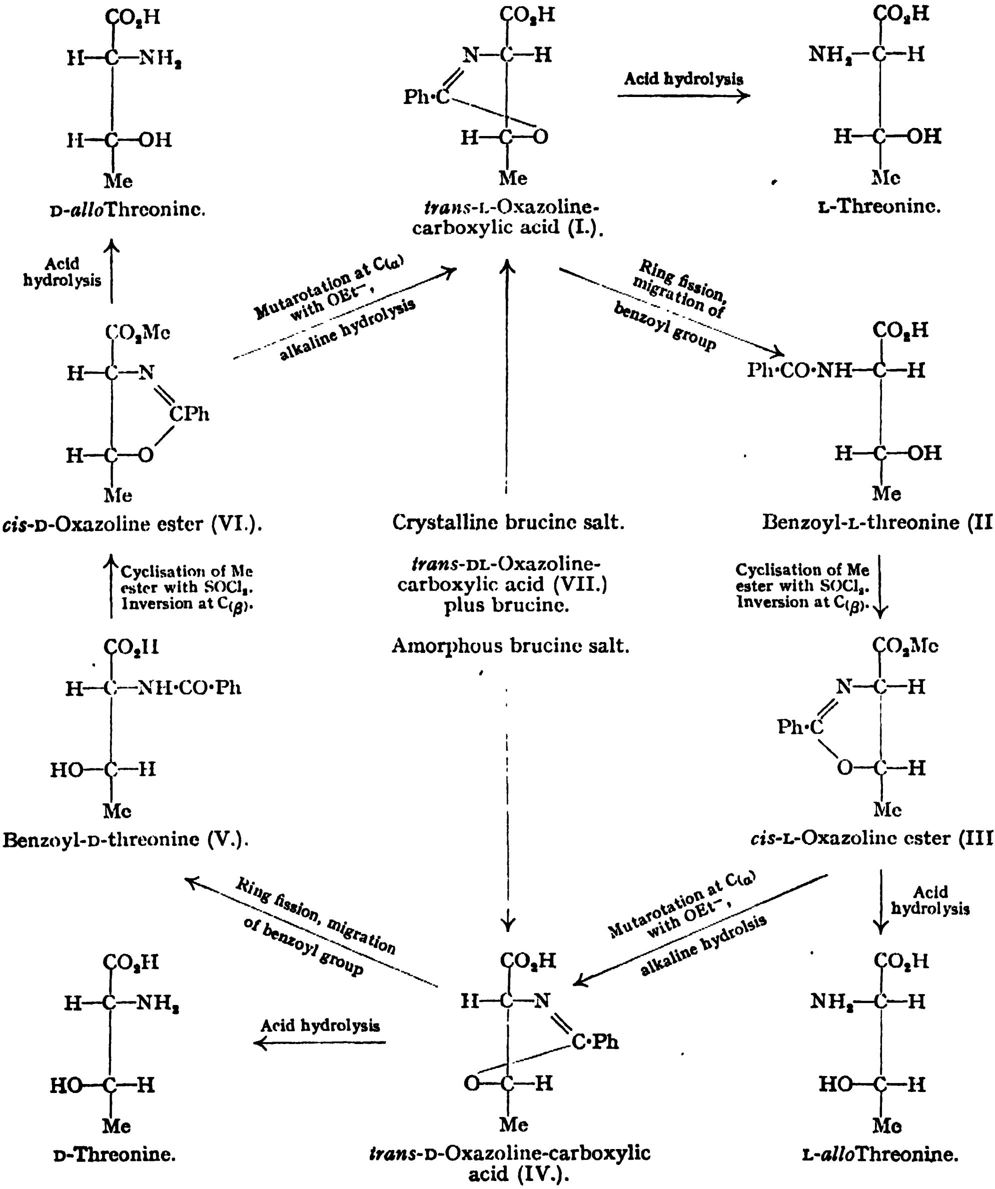
In a previous paper (Elliott, *J.*, 1949, 589) it was shown that both stereoisomeric DL-forms of ethyl 2-phenyl-5-methyl-Δ^2-oxazoline-4-carboxylate gave, on hydrolysis with aqueous alkali, the *trans*-acid which is configurationally related to threonine. As a result of this discovery the overall yield of DL-threonine obtained in the synthesis from hippuric acid (Attenburrow, Elliott, and Penny, *J.*, 1948, 310) was considerably increased. It was apparent from the data accumulated in this work that it should be possible to evolve a cycle of asymmetric transformations for the interconversion of the four stereoisomers of α-amino-β-hydroxybutyric acid (cf. Elliott, *Nature*, 1948, **162**, 657). The conversion of D-threonine into its optical antipode was particularly desirable. Realisation of these possibilities depended on the asymmetry of the molecule being retained during the cyclisation of ethyl α-benzamido-β-hydroxybutyrate with thionyl chloride which was described in a previous paper (Elliott, 1949, *loc. cit.*). Owing to the presence of two asymmetric centres it was not possible to obtain unequivocal evidence on this point by working with the racemic substances. It could always be argued that the inversion took place through an optically inactive intermediate by destruction, followed by regeneration, of both centres of asymmetry.

Resolution of DL-*N*-formyl-*O*-methylthreonine has been described by West and Carter (*J. Biol. Chem.*, 1937, **119**, 109); this compound is not easily accessible from threonine itself, but only from crotonic acid. The main aim of the present investigation being to find a convenient synthesis of L-threonine from hippuric acid with the minimum number of steps it was desirable to resolve one of the intermediate compounds. This task proved to be exceedingly difficult. DL-*N*-Benzoylthreonine received a great deal of attention with complete lack of success. It gave non-crystalline salts with brucine, quinine, cinchonine, and ψ-ephedrine, whereas with 1-phenylethylamine it gave sparingly soluble diastereo-compounds in a variety of solvents. DL-N-*Formyl*-O-*benzoylthreonine* prepared from DL-*O*-benzoylthreonine in the usual way also gave a diastereo-compound with (—)-1-phenylethylamine. Mild alkaline hydrolysis of DL-*N*-formyl-*O*-benzoylthreonine gave DL-N-*formylthreonine* which was a very soluble compound and could not be resolved. Various other derivatives were tried without success. At this point the choice was becoming limited and it was decided to investigate the resolution of *trans*-DL-2-phenyl-5-methyl-Δ^2-oxazoline-4-carboxylic acid (VII). This compound was the last to be considered because of its instability; it was known to be sensitive to dilute mineral acid (Elliott, 1949, *loc. cit.*). Considerable time was devoted to the resolution of the oxazolinecarboxylic acid with (+)- and (—)-1-phenylethylamine because it would then have been possible to obtain both forms in a state of purity. Although partial success was achieved this resolution was abandoned when it was found that recrystallisation of the salts, even in anhydous solvents, resulted in fairly extensive decomposition. This was attributed to an attack on the cyclic imino-ether group by the primary amine to produce an open-chain amidine derivative (cf. Barber, Gregory, Slack, Stickings, and Woolman, *CPS.* 66, May 24th, 1944). It was obvious that only tertiary bases could be used with safety in this case. (—)-Ethyl-1-phenyldimethylamine (Snyder and Brewster, *J. Amer. Chem. Soc.*, 1949, **71**, 291) did not give a crystalline salt with the oxazoline-carboxylic acid.

Success was finally achieved with brucine as the resolving base. Fortunately only one of the diastereoisomeric salts crystallised and this was extremely well defined. It was quite stable in anhydrous solvents, possessed very satisfactory solubility properties, and was formed in high yield. Furthermore, the acid combined with the brucine was trans-L-2-*phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylic acid* (I), because it yielded L-threonine on acid hydrolysis. It then remained to test out the ideas concerning the interconversion of the stereoisomeric forms which were mentioned above. The brucine salt remaining in solution was decomposed with dilute alkali and chloroform, and the crude D-oxazolinecarboxylic acid (IV) converted in solution without isolation into *N*-benzoyl-D-threonine (V) through the *O*-benzoyl derivative. Polarimetric investigation revealed that not less than 70% of the crude product was the D-form. The benzoyl compound was esterified with diazomethane and cyclised with thionyl chloride at 0°. The oxazoline ester obtained had a high optical rotation; this ruled out the possibility that the crotonic acid derivative, $CHMe{:}C(NH{\cdot}CO{\cdot}Ph){\cdot}CO_2Me$ was an intermediate in the cyclisation. Although this had always been considered remote, it is the first time that definite evidence has been obtained on this point. Previous work has shown that the action of thionyl chloride on ethyl α-benzamido-β-hydroxybutyrate causes cyclisation with inversion at $C_{(\beta)}$. The oxazoline ester obtained from impure (V) must therefore have consisted of not less than 70% of the *cis*-D-form (VI), the remainder being the *cis*-L-form (III). According to experiments described in a previous paper (Elliott, 1949, *loc. cit.*) mild hydrolysis of this mixture with aqueous alkali should have caused mutarotation at $C_{(\alpha)}$, thus giving the corresponding *trans*-forms. This was not the case. A complex mixture resulted from which only a small quantity of the *trans*-L-form (I) was isolated as the brucine salt. DL-*N*-Benzoyl*allo*threonine was also isolated from this mixture. Clearly, incomplete mutarotation had occurred at $C_{(\alpha)}$. The earlier experiments referred to above had been carried out on the ethyl *cis*-DL-oxazoline ester, mutarotation appearing to be complete. Failure to obtain the same results with the corresponding optically active methyl ester was attributed to the much faster rate of hydrolysis of this compound. It seemed probable that mutarotation ceased as soon as the ester group had been removed.

In order to gain further information concerning the rate of this mutarotation under various conditions, experiments were conducted on *methyl* cis-L-2-*phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylate* (III) which was readily obtainable in pure form. Pure benzoyl-L-threonine (II) was prepared from the brucine salt of (I) and was esterified with diazomethane. The *benzoyl*-L-*threonine methyl* ester was cyclised with thionyl chloride to give the pure oxazoline ester

(III) in good yield. Mutarotation studies on this compound were carried out polarimetrically. In a mixture of equal parts of N-sodium hydroxide and alcohol mutarotation occurred to a much greater extent than with aqueous alkali, but conversion into (IV) was still not complete. This was the case even when the alkali was present in excess, showing that the free acid corresponding



D-*allo*Threonine.
trans-L-Oxazoline-carboxylic acid (I.).
Acid hydrolysis
L-Threonine.
Acid hydrolysis
Mutarotation at C(α) with OEt⁻, alkaline hydrolysis
Ring fission, migration of benzoyl group
cis-D-Oxazoline ester (VI.).
Crystalline brucine salt.
Benzoyl-L-threonine (II.).
Cyclisation of Me ester with SOCl₂. Inversion at C(β).
trans-DL-Oxazoline-carboxylic acid (VII.) plus brucine.
Cyclisation of Me ester with SOCl₂. Inversion at C(β).
Amorphous brucine salt.
Benzoyl-D-threonine (V.).
cis-L-Oxazoline ester (III.).
Ring fission, migration of benzoyl group
Mutarotation at C(α) with OEt⁻, alkaline hydrolsis
Acid hydrolysis
Acid hydrolysis
D-Threonine.
trans-D-Oxazoline-carboxylic acid (IV.).
L-*allo*Threonine.

In this scheme the prefixes D- or L- refer to the configuration at $C_{(\alpha)}$ as in all amino-acids, but the projection formulæ are those conventionally used for carbohydrates.

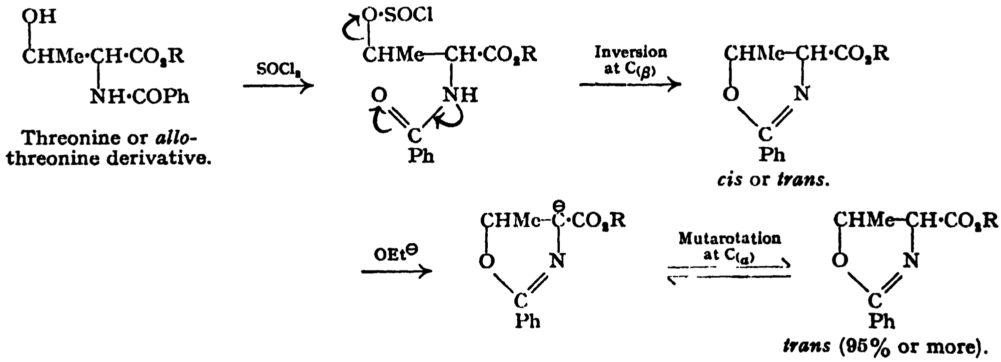
to (III) did not undergo mutarotation. In alcoholic sodium ethoxide solution at room temperature mutarotation was immeasurably fast; after addition of water to the solution, followed by short refluxing to hydrolyse the ester group, the rotation of the solution revealed that about 95% conversion into the *trans*-D form (IV) had occurred.

Application of these experimental conditions to the impure *cis*-D-oxazoline ester (VI), obtained from the amorphous brucine salt as described above, gave the desired result. The

yield of (I) isolated as the brucine salt from the product was approximately that expected from the specific rotation of the crude benzoyl-D-threonine. The total yield of brucine salt obtained from the resolution of the oxazoline-carboxylic acid and from the inversion of the D-form was about 75% (based on the utilisation of both forms) of slightly impure material. It was recrystallised twice with a loss of 10—15%. The overall yield of L-threonine from hippuric acid was 22%; this could have been raised by re-utilisation of the mother-liquors, but for ordinary preparative work this seemed hardly necessary. Recently, Pfister, Robinson, Shabica, and Tishler (*J. Amer. Chem. Soc.*, 1949, **71**, 1101) have described a synthesis of DL-threonine in good overall yield from acetoacetic ester, and in a later paper from the same laboratories (Zambito, Peretz, and Howe, *ibid.*, p. 2541) resolution through the *p*-nitrobenzoyl derivative is reported. Although it was known that the resolution of DL-*p*-nitrobenzoylserine had been accomplished by Fischer and Jacobs (*Ber.*, 1906, **39**, 2942) this method of resolving DL-threonine was not investigated in this laboratory because it would have added extra stages to the synthesis. Fortunately, the present investigation was greatly simplified by the successful resolution of the oxazoline-carboxylic acid, which lies directly on the synthetic pathway from hippuric acid. It must be admitted that the oxazoline-carboxylic acid is not an ideal substance for resolution because of its instability, but by careful attention to experimental detail this disadvantage can be overcome.

The *trans*-L-oxazoline-carboxylic acid (I), which can be obtained absolutely pure as the brucine salt, is the key substance from which all four stereoisomers of α-amino-β-hydroxybutyric acid were prepared as shown in the reaction scheme. The yields were good at every stage. It has been shown (Elliott, 1949, *loc. cit.*) that the ethyl ester hydrochlorides of threonine or *allo*threonine are converted into the corresponding oxazoline esters with retention of configuration at both asymmetric centres on treatment with benzimino ethyl ether. Thus it is possible to leave and re-enter the main pathway (I to VI) at will; all four stereoisomers are therefore easily interconvertible. This cycle of interconversions establishes the configurations of the *allo*threonines relative to L-threonine. L-*allo*Threonine was dextrorotatory in water and much more so in N-HCl. This increase in positive rotation on conversion into the cation is in agreement with Clough's rule concerning naturally occurring amino-acids (Clough, *J.*, 1915, **107**, 1509; 1918, **113**, 526). The preparation of D- and L-*allo*threonine was first carried out by West and Carter (*J. Biol. Chem.*, 1938, **122**, 611). The specific rotations of these substances prepared by the present method are in good agreement with those recorded by West and Carter.

The asymmetric transformations described in this paper can be explained satisfactorily by the reaction mechanisms previously proposed by the author which are summarised below:



The term mutarotation has been applied to the inversion of configuration which occurs when the *cis*-oxazoline esters are brought into contact with ethoxide ions. It is believed that this expression correctly describes the phenomenon, because the final product is probably an equilibrium mixture containing a small but definite amount of the *cis*-isomer. The evidence from the polarimetric study is that at least 95% of the *trans*-form was present after equilibration and hydrolysis. No figures were available for the rotation of the corresponding *cis*-oxazoline-carboxylic acid, but as judged by the figures for the rotation of the methyl esters the sign would have been opposite to that for the *trans*-form. The fact that the optical rotation did not reach the theoretical figure after equilibration could be explained by decomposition to optically inactive substances, or to the presence of a very small quantity of the *cis*-form. The remarkable stereochemical specificity of this reaction must be attributed to powerful steric forces.

EXPERIMENTAL.

(M. p.s are uncorrected.)

DL-N-*Formyl*-O-*benzoylthreonine*.—Ethyl DL-*trans*-2-phenyl-5-methyl-Δ^2-oxazoline-4-carboxylate (2·3 g.) was refluxed with 0·5N-sodium hydroxide (22 ml.) until dissolved, and then cooled to room temperature, and 5N-hydrochloric acid (4·2 ml., 2 equivs.) was added. After 4 hours hydrated sodium acetate (1·4 g.) was added with stirring. The main bulk of the *O*-benzoylthreonine separated rapidly. It was filtered off; the mother-liquors were evaporated to obtain a second crop and were finally evaporated to dryness under reduced pressure. The solids were combined, mixed with 90% formic acid (10 ml.), and warmed to 45°, and acetic anhydride (3 ml.) was added dropwise with shaking. The solution was then heated to 80° for 15 minutes and evaporated to dryness under reduced pressure. The residue was lixiviated with cold water to remove sodium chloride and dried at 100°. DL-N-*Formyl*-O-*benzoylthreonine* (1·9 g., 76%) formed irregular masses of prisms (from hot water), m. p. 172—173° (Found: C, 57·3; H, 5·25; N, 5·85. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2; N, 5·6%).

The salt with (+)-1-phenylethylamine had m. p. 154—155°. The *N*-formyl-*O*-benzoylthreonine liberated on addition of acid to an aqueous solution of this salt was optically inactive.

DL-N-*Formylthreonine*.—The corresponding *O*-benzoyl compound (1·9 g.) was suspended in water (10 ml.), and 5N-sodium hydroxide added dropwise until the acid was neutralised. An additional 1·65 ml. of 5N-sodium hydroxide was then added and the solution set aside 30 minutes at room temperature The solution was then treated with 5N-hydrochloric acid (3·1 ml.), the benzoic acid was filtered off, and the filtrate extracted thoroughly with light petroleum. The aqueous layer was evaporated to dryness under reduced pressure, the residue was extracted with warm ethanol (20 ml.) and filtered from sodium chloride, and the filtrate again evaporated to dryness. The residue was dissolved in dry dioxan, a small amount of resinous material was filtered off, and the solvent removed under reduced pressure. The residual oil was dissolved in a small quantity of anhydrous ethanol, and anhydrous ether was added until a cloudiness was produced. On storage at 0° DL-N-*formylthreonine* (0·4 g., 36%) separated in heavy prisms, m. p. 104°. It was recrystallised from ethanol–ether and then had m. p. 105—106°, which changed to 125—126° during storage for several weeks in a closed tube (Found: C, 41·0; H, 6·7; N, 9·3. $C_5H_9O_4N$ requires C, 40·8; H, 6·2; N, 9·5%). Owing to the unsatisfactory yield of this substance, attempts at resolution were abandoned after a few unsuccessful experiments.

DL-trans-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylic Acid* (VII).—This compound may be prepared from the corresponding pure ethyl *trans*-oxazoline ester (obtained from DL-threonine ethyl ester hydrochloride and benzimino ethyl ether), in which case the yield was 87%, or from the mixture of *cis*- and and *trans*-oxazoline esters obtained in the synthesis of DL-threonine from hippuric acid, as follows. The mixture of esters obtained as described by Elliott (1949, *loc. cit.*) was distilled and the fraction of b. p. 110—130°/0·05 mm. collected. The yield of purified product was 75% calculated on crude ethyl α-benzamido-β-hydroxybutyrate. The ester mixture (46·6 g.) was added to N-sodium hydroxide (220 ml.); after addition of ethanol (220 ml.) the solution was refluxed for 15 minutes and then evaporated to 150—200 ml. under reduced pressure. The solution was cooled to 0° in an alcohol–solid carbon dioxide bath and efficiently stirred whilst 5N-hydrochloric acid (*ca.* 44 ml.) was added dropwise, the temperature being maintained at 0° throughout; the addition of the acid required 20—30 minutes. Local excess of acid was carefully avoided. The pH of the solution was tested from time to time by means of Johnson's universal indicator paper, and when it had fallen to 3·5—4·0 the addition of acid was stopped. Generally, about 90% of the theoretical amount of acid was required. The oxazolinecarboxylic acid usually began to crystallise before the addition of hydrochloric acid was complete; when it was delayed, the solution was seeded and the sides of the vessel were scratched. After the addition of hydrochloric acid was complete the solution was stirred for 15 minutes at 0° with occasional scratching of the vessel to complete the crystallisation. The acid was filtered by suction, washed with a small quantity of ice-water, and dried as quickly as possible over sodium hydroxide and concentrated sulphuric acid in an efficient vacuum. The acid appeared to be quite stable when dry. The yield was 28·5 g. (71%) and the m. p. 134—137°. This material was pure enough for further work.

trans-L-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylic Acid* (I).—(a) *Resolution of the* DL-*acid*. The acid (28·4 g.) was added to a solution of anhydrous brucine (54·5 g.) in dry ethanol (110 ml.), and the mixture heated until all or most of the solid had dissolved. Anhydrous ethyl acetate (250 ml.; distilled over phosphoric oxide) was then added and heating continued if necessary. After a further addition of dry ethyl acetate (300 ml.) the solution was kept at 0° with exclusion of moisture for 4 days. The crop of crystalline solid was filtered off and washed with a little anhydrous ethyl acetate. The mother-liquors and washings were evaporated to dryness under reduced pressure at a temperature not exceeding 45°. The residue was dissolved in a mixture of anhydrous ethanol (16 ml.) and anhydrous ethyl acetate (80 ml.) and kept at 0° for 3 days. The second crop was treated as before. The total yield of slightly impure brucine salt was 35·6 g. (82%). The m. p. of the salt was variable; melting was generally over a 2° range between the limits 128° and 140°. Crystallisation of the salt from aqueous methanol or ethanol gave a salt, m. p. 162—164°, but some decomposition (of unknown nature) to an oily substance also occurred. Crystallisation of the salt from anhydrous ethanol, on the other hand, gave an excellent recovery of crystalline material. The m. p. was again somewhat variable: in 3 separate experiments, 128°, 131—132°, and 132—133°. It was established that there was no difference in the purity of the three samples, by decomposition, as described below, to L-threonine which in every case had the correct specific rotation. The impure brucine salt (35·6 g.) was crystallised twice from anhydrous ethanol (180 ml. and 160 ml. respectively). The yield of pure salt was 31 g. (70%). Analysis showed that the pure salt contained one molecule of alcohol of crystallisation (Found: C, 66·2; H, 6·7; N, 6·7. $C_{34}H_{37}O_7N_3,C_2H_5OH$ requires C, 67·0; H, 6·7; N, 6·5%). $[\alpha]_D^{25}$ was +13·6° (*c*, 6 in chloroform).

(b) *Inversion of the* D-*isomer.* The mother-liquors from the resolution and from the crystallisation of the salt were combined and evaporated to dryness under reduced pressure below 45°. The residual frothy mass was shaken with N-sodium hydroxide (100 ml.) and chloroform (200 ml.) until completely dissolved. The aqueous layer was extracted twice more with chloroform, the chloroform extracts were combined and washed once with water, and the two aqueous layers combined. To the aqueous solution was then added 5N-hydrochloric acid (*ca.* 38 ml.) with stirring to pH 1 (glass electrode). This caused ring fission of the D-oxazoline-carboxylic acid to D-*O*-benzoylthreonine. After 4 hours at room temperature 5N-sodium hydroxide (*ca.* 36 ml.) was added to the solution with stirring until alkalinity to phenophthalein was attained. The *O*-benzoyl-D-threonine separated as a crystalline solid halfway through the neutralisation and then redissolved. The solution of crude *N*-benzoyl-D-threonine was acidified (Congo-red) with concentrated hydrochloric acid and extracted 6 times with an equal volume of ethyl acetate. The combined ethyl acetate extracts were shaken with a small quantity of anhydrous sodium sulphate, filtered, and evaporated to small bulk under reduced pressure. The benzoyl compound rapidly crystallised. It was filtered off and washed with a little ethyl acetate. The mother-liquors were evaporated to dryness under reduced pressure and kept over concentrated sulphuric acid and sodium hydroxide in a vacuum desiccator until quite solid. The two crops of solid (18 g., 89%) were mixed and ground together in a mortar. $[\alpha]_D^{21}$ was −12·75° (*c*, 1·7 in water).

The solid was suspended in ether (200 ml.) and esterified by careful addition, with shaking, of an ethereal solution of diazomethane in slight excess. On evaporation of the ether the crude methyl ester remained as a syrup which rapidly solidified; it was dried in a vacuum desiccator over concentrated sulphuric acid. The yield was 18·55 g. (97%).

The powdered methyl ester was added in small portions, with stirring, to thionyl chloride (53 ml.; purified by distillation over quinoline and linseed oil) which was cooled to 0—5°. The temperature was not allowed to rise above 5° during the addition. The mixture was allowed to stand overnight at 0°; excess of thionyl chloride was then removed under diminished pressure below 35°. The residue, which frequently crystallised, was dissolved in dry chloroform and without delay the solution was poured slowly into sodium carbonate solution (10%; 250 ml.) with efficient stirring. If necessary, addition of solid sodium carbonate was made to prevent the solution becoming acid. The chloroform layer was separated, the aqueous layer was extracted once more with chloroform, and the combined chloroform extracts were washed with water, dried and distilled. The product (14·3 g., 83·5%) had b. p. 110—115°/0·03 mm., $[\alpha]_D^{25}$ −36·7° (*c*, 4·5 in ethanol). This was a mixture of the two methyl *cis*-oxazoline esters (III) and (VI), containing about 70% of the latter.

The mixture was dissolved in dry ethanol (69 ml.), and to it was added a solution of sodium (1·58 g.; 5% excess over 1 mol.) in dry ethanol (69 ml.). After the solution had been kept for 5 minutes at room temperature, water (138 ml.) was added and the mixture refluxed for 15 minutes. The solution was evaporated under reduced pressure to about 50 ml. and cooled to 0°, and 5N-hydrochloric acid (13·7 ml.; exactly equivalent to the sodium used) added dropwise with stirring, with the precautions referred to above in the isolation of the DL-oxazolinecarboxylic acid from its sodium salt. The product (11·55 g., 86·5%), m. p. 151—154° with previous softening, was a mixture of the *trans*-oxazolinecarboxylic acids (IV) and (I) containing about 70% of the latter. The acid was added to a solution of anhydrous brucine (22·2 g.) in anhydrous ethanol (160 ml.) and heated until dissolved. The crystalline brucine salt (29·1 g., 72% calc. on the methyl oxazoline ester), m. p. 126—128°, separated on cooling. It was recrystallised twice from absolute ethanol (*ca.* 5 parts), giving 24·9 g. of pure salt, m. p. 127—129°.

The total yield of pure brucine salt from (*a*) and (*b*) was 55·9 g. (62·5%, calc. on the oxazolinecarboxylic acid).

The salt (27·4 g.) was decomposed with N-sodium hydroxide (50 ml.) and chloroform in the usual way, and the aqueous layer cooled to 0° and treated with 5N-hydrochloric acid (10 ml.) with the usual precautions. trans-L-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylic acid* separated in small hexagonal plates (7·1 g., 78%), m. p. 162—163°, $[\alpha]_D^{27}$ +109·8° (*c*, 10 in 1 : 1 ethanol–N-aqueous sodium hydroxide), +108·2° (*c*, 6·25 in the same solvent) (Found : N, 6·7. $C_{11}H_{11}O_3N$ requires N, 6·8%).

N-*Benzoyl*-L-*threonine* (II).—The corresponding *trans*-L-oxazoline-carboxylic acid was dissolved in 1 equivalent of N-hydrochloric acid at room temperature, and after 4 hours at room temperature the solution was back-titrated with alkali etc., as described above for the preparation of crude benzoyl-D-threonine. Benzoyl-L-threonine was formed in almost theoretical yield. Recrystallised from ethyl acetate it had m. p. 146—148°, $[\alpha]_D^{25}$ +25·8 (*c*, 1·4 in water). West and Carter (1937, *loc. cit.*) recorded $[\alpha]_D^{26}$ +25·1 (in water). *Benzoyl*-L-*threonine methyl ester*, prepared (93%) in the usual way with diazomethane and crystallised from ether, had m. p. 96°, $[\alpha]_D^{26}$ +23·2° (*c*, 5·4 in ethanol) (Found : N, 6·1. $C_{12}H_{15}O_4N$ requires N, 5·9%).

Methyl cis-L-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylate* (III).—Benzoyl-L-threonine methyl ester (7 g.) was cyclised with thionyl chloride (20 ml.) at 0° as described above for crude benzoyl-D-threonine methyl ester. The yield of *oxazoline* ester, b. p. 110—115°/0·01 mm., was 6 g. (93%). It solidified on storage to a colourless solid which was crystallised from light petroleum (b. p. 40—60°), forming dense prisms, m. p. 74—75°, $[\alpha]_D^{27}$ +69·2° (*c*, 8·5 in ethanol) (Found : N, 6·7. $C_{12}H_{13}O_3N$ requires N, 6·4%).

Polarimetric Investigations of the Mutarotation and Hydrolysis of Methyl cis-L-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylate.*—Aqueous alcoholic sodium hydroxide was prepared by diluting N-sodium hydroxide (50 ml.) to 100 ml. with ethanol. The oxazoline ester (1·095 g., 0·005 mol.) was dissolved in the sodium hydroxide solution (11 ml.). Unfortunately the rotation could not be measured at once because of a cloudiness which developed. After centrifugation in a stoppered tube the solution was placed in a 1-dm. polarimeter tube. Zero time was arbitrarily chosen as the instant when all the oxazoline ester had dissolved in the sodium hydroxide solution. The following readings were obtained at 23° (zero of instrument 360°) (the second place of decimals was not considered significant in this rough experiment) :

After 8 mins.	352·2°	After boiling for 2 mins.	352·0°
After 51·5 mins.	352·2	After boiling for 15 mins.	352·0

It was known that hydrolysis of the ester group would certainly be complete after 15 minutes' boiling. The final rotation of the solution should have been −10·2° instead of −8·0° if complete conversion into the *trans*-isomer had occurred. From the very small change in rotation that took place after the first 8 minutes it seemed probable that hydrolysis was complete in this time. To test whether further mutarotation took place after hydrolysis in the presence of excess of alkali, a portion of the above solution was diluted with the 0·5N-aqueous-alcoholic sodium hydroxide and the rotation of the solution measured before and after 15 minutes' boiling. There was no change in the rotation of the solution, which had the expected value when allowance was made for the dilution.

The oxazoline ester (1·095 g.) was dissolved in anhydrous ethanol (10 ml.) containing exactly 1 equivalent of sodium ethoxide. Polarimeter readings were taken in a 1-dm. tube at 24—25°. After 4 minutes from zero time which was arbitrarily chosen as before, the reading was 350·8° and no further change took place on storage for one hour. The ester in solution was hydrolysed by addition of water (10 ml.), followed by boiling for 15 minutes. The rotation of the solution was then −5·0°. For complete conversion into the *trans*-isomer it should have been −5·6°. From the rotation of the methyl *cis*-L-oxazoline ester it seemed probable that the *cis*-L-oxazolinecarboxylic acid would possess a high rotation opposite in sign to that of the *trans*-L-oxazolinecarboxylic acid. On the basis of this assumption the extent of the conversion was approx. 95%.

L-allo*Threonine.*—The methyl *cis*-L-oxazoline ester (2 g.) was refluxed 5 hours with 6N-hydrochloric acid (20 ml.), the solution was cooled, extracted with ether to remove benzoic acid, and evaporated to dryness under reduced pressure. The residual syrup was dissolved in hot ethanol (20 ml.) and excess of pure pyridine added. On cooling L-*allo*threonine separated as dense prisms (1·05 g., 96%). It was recrystallised from 50% aqueous ethanol and had m. p. 273—274° (decomp.), $[\alpha]_D^{24}$ +9·3° (*c*, 3·8 in water), and $[\alpha]_D^{27}$ +32·5° (*c*, 8·2 in N-hydrochloric acid) (Found: N, 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%). West and Carter (1938, *loc. cit.*) recorded $[\alpha]_D^{26}$ +9·6° (in water) for their dextrorotatory isomer.

trans-D-2-*Phenyl-5-methyl-Δ²-oxazoline-4-carboxylic Acid* (IV).—The methyl *cis*-L-oxazoline ester (III) was treated with sodium ethoxide, etc., as described above for the crude D-isomer. The *trans*-D-acid had m. p. 163—164° and $[\alpha]_D^{23}$ −106·1° (*c*, 5·4 in 1 : 1 ethanol–N-aqueous sodium hydroxide).

N-*Benzoyl*-D-*threonine* (V).—The methyl *cis*-L-oxazoline ester (III) (7·9 g.) was treated with sodium ethoxide, etc., as described above except that the oxazoline-carboxylic acid was not isolated but was converted in solution into *N*-benzoyl-D-threonine in the usual way (see above). The product was recrystallised from ethyl acetate. The pure material (6 g., 75%) had m. p. 145—146° and $[\alpha]_D^{28}$ −25·1° (*c*, 1·5 in water) (Found: N, 6·0. Calc. for $C_{11}H_{13}O_4N$: N, 6·3%). West and Carter (1937, *loc. cit.*) recorded $[\alpha]_D^{26}$ −25 5° (in water) for this compound. *Benzoyl*-D-*threonine methyl ester*, prepared with diazomethane in the usual way, had m. p. 96°, $[\alpha]_D^{26}$ −23·3° (*c*, 6 in ethanol) (Found: N, 5·9. $C_{12}H_{15}O_4N$ requires N, 5·9%).

D-*Threonine.*—In this case the amino-acid was prepared from benzoyl-D-threonine and not from (IV) as shown in the chart. The benzoyl compound (2 g.) was hydrolysed as in the preparation of L-*allo*threonine. D-Threonine (yield, 0·95 g., 89%) formed aggregates of hexagonal plates (from 80% ethanol), m. p. 264° (decomp.), $[\alpha]_D^{25}$ +28·4° (*c*, 4·4 in water) (Found: N, 11·5. Calc. for $C_4H_9O_3N$: 11·8%). West and Carter (1937, *loc. cit.*) gave $[\alpha]_D^{26}$ +28·4° (in water).

Methyl cis-D-2-*Phenyl-5-methyl-Δ²-oxazoline-4-carboxylate* (VI).—This *ester* was prepared from benzoyl-D-threonine methyl ester, as described for the L-isomer, in 88% yield. It had m. p. 75—76°, $[\alpha]_D^{25}$ −68·9° (*c*, 8·4 in ethanol) (Found: N, 6·6. $C_{12}H_{13}O_3N$ requires N, 6·4%).

D-allo*Threonine.*—This substance was prepared from (VI) in the usual way, in 94% yield. It had m. p. 272—273° (decomp.), $[\alpha]_D^{25}$ −9·1° (*c*, 3·9 in water) (Found: N, 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%). West and Carter (1938, *loc. cit.*) gave $[\alpha]_D^{26}$ −9·11° (in water).

L-*Threonine.*—The pure brucine salt of the *trans*-L-oxazolinecarboxylic acid (I) (109 g.) was decomposed with N-sodium hydroxide (200 ml.) and chloroform in the usual way. To the aqueous layer was then added 10N-hydrochloric acid (440 ml.), the solution was diluted to 700 ml., and the mixture was refluxed for 5 hours. After cooling, benzoic acid was removed by one extraction with ether, and the aqueous layer was evaporated to dryness under diminished pressure. The residue was extracted with hot ethanol (99%; 400 ml.), the solution was filtered from sodium chloride, and pyridine (25 ml.) added to the filtrate. After 24 hours at 0° the L-threonine {17 g., 85%; $[\alpha]_D^{28}$ −27·45° (*c*, 2·8 in water)} was collected and washed with absolute alcohol. It was crystallised from 80% ethanol and formed hexagonal plates, m. p. 262—263° (decomp.), $[\alpha]_D^{27}$ −28·3° (*c*, 6 in water), $[\alpha]_D^{21}$ −28·5° (*c*, 2·4 in water) (Found: N, 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%). West and Carter (1937, *loc. cit.*) recorded $[\alpha]_D^{26}$ −28·3° (in water). The yield of pure amino-acid was 16 g. (80% calc. on the brucine salt.).

The author thanks Mr. V. G. Sheppard for experimental assistance.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
HAMPSTEAD, N.W.3.

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16. *Acetylene Reactions. Part VI. Trimerisation of Ethynyl Compounds.*

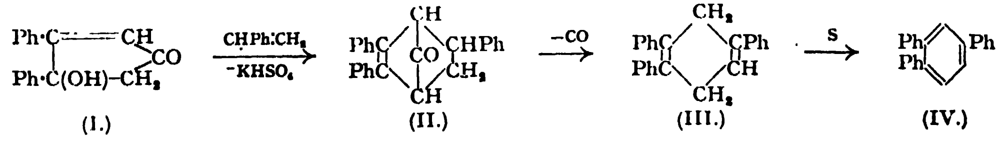
By J. D. Rose and F. S. Statham.

Dicarbonyldi(triphenylphosphino)nickel catalyses the polymerisation of phenylacetylene to the hitherto unknown 1 : 2 : 4-*triphenylbenzene*, the structure of which is demonstrated by unambiguous synthesis. Phenylethynylcarbinol is trimerised to 1 : 3 : 5-*tri*-(*α-hydroxybenzyl*)-*benzene*, which is oxidised to the known 1 : 3 : 5-tribenzoylbenzene.

Information from Germany after the end of the war (cf. F.I.A.T. Final Report No. 933, H.M.S.O., London, 1946) contains references to a catalyst, dicarbonyldi(triphenylphosphino)nickel, of the composition $(Ph_3P)_2Ni(CO)_2$, alleged to be active in the synthesis of acrylic acid derivatives from acetylenes and nickel carbonyl. A sample of this catalyst had been prepared in these laboratories, and on the appearance of the paper by Reppe and Schweckendiek (*Annalen*, 1948, **560**, 104) which contains, *inter alia*, an account of the trimerisation of propargyl alcohol by this catalyst to a mixture of 1 : 2 : 4- and 1 : 3 : 5-tri(hydroxymethyl)benzene, the trimerisation of a series of acetylenic compounds was investigated.

The catalyst is prepared by interaction of triphenylphosphine (2 moles) and nickel carbonyl (1 mole) in ether and separates as a pale cream-coloured crystalline powder which cannot be recrystallised without decomposition. From its solution in cold benzene nickel hydroxide is precipitated within a day or two and, although reasonably good analytical figures are obtained on a freshly prepared sample, after six months' storage the carbon content increases and the nickel content falls considerably; the catalytic activity also falls off markedly on storage.

Of a range of compounds investigated, only three acetylenic compounds were successfully trimerised; propargyl alcohol (see Reppe and Schweckendiek, *loc. cit.*), phenylethynylcarbinol (1-phenylpropargyl alcohol), and phenylacetylene. Phenylethynylcarbinol in boiling methyl alcohol was slowly trimerised to 1 : 3 : 5-*tri*-(*α-hydroxybenzyl*)*benzene*, the structure of which was demonstrated by its oxidation to the known *s*-tribenzoylbenzene. The polymerisation of phenylacetylene by the catalyst was violent and, unless the compound was diluted with a large volume of alcohol, was almost explosive. In 10% alcoholic solution, polymerisation is vigorous and exothermic, but can be controlled. The crude product, an orange-brown gum, was purified by distillation and repeated crystallisation, giving a white crystalline solid, m. p. 109°, with the molecular weight and the composition of a triphenylbenzene. Of the three theoretically possible triphenylbenzenes, only the 1 : 2 : 3-, m. p. 157° (Smith, *Ber.*, 1893, **26**, 65), and the 1 : 3 : 5-isomer, m. p. 170° (Vorländer, Fischer, and Wille, *Ber.*, 1929, **62**, 2836), are known. The hydrocarbon, m. p. 109°, was clearly different from either of these; the m. p. of *s*-triphenylbenzene was depressed to 80°—90° on admixture, and the formation of 1 : 2 : 3-triphenylbenzene would be very improbable, involving as it would the migration of a phenyl radical under relatively mild conditions. By elimination, therefore, it appeared probable that the substance in hand was the hitherto unknown 1 : 2 : 4-*triphenylbenzene*. This was established by synthesis, as follows



4-Hydroxy-3 : 4-diphenyl*cyclo*pent-2-en-1-one (I) (Japp and Miller, *J.*, 1885, 27) ("anhydromonoacetone benzil"), when heated with styrene in the presence of potassium hydrogen sulphate as dehydrant, affords the adduct 3 : 6-endo*keto*-1 : 2 : 4-*triphenyl*cyclo*hex*-1-*ene* (II), which on being heated above its melting point loses carbon monoxide and gives (presumably) a triphenyldihydrobenzene (*e.g.*, III), which could not be obtained crystalline but which, when dehydrogenated with sulphur, gave 1 : 2 : 4-triphenylbenzene (IV) identical with that obtained by polymerisation of phenylacetylene. Attempts to simplify the synthesis by interaction of (I) and phenylacetylene, which should have given (IV) more directly, *via* the (unstable) doubly unsaturated analogue of (II), were unsuccessful.

The formation of 1 : 2 : 4-triphenylbenzene unaccompanied by the 1 : 3 : 5-isomer is peculiar; Krasouskii and Kipryanov (*J. Phys. Chem. Russia*, 1925, **56**, 1; from *Chem. Abs.* 1925, **19**, 2817) showed that phenylacetylene, when heated with methylamine or ethylamine at 250—260° for 5—6 hours (sealed tube), affords *s*-triphenylbenzene. It is virtually certain that the *s*-isomer is not formed in the polymerisation described here; its solubility is much lower than that of the 1 : 2 : 4-isomeride, and it is clear that if both were formed together, the *s*-isomeride would be the more easily isolated. Attempted trimerisation of a variety of other ethynyl compounds, including 3-methylbut-1-yn-3-ol, 3-diethylaminobut-1-yne, benzoylacetylene, and phenylpropiolic acid, all failed or gave non-crystalline products which could not be identified.

EXPERIMENTAL.

Dicarbonyldi(triphenylphosphino)nickel, $[(CO)_2Ni(Ph_3P)_2]$.—Triphenylphosphine (13·1 g.) in ether (30 c.c.) was refluxed gently on the steam-bath, and nickel carbonyl (4·2 g.; 3·2 c.c.) was gradually added. Carbon monoxide was evolved briskly and, after addition of half of the nickel carbonyl, crystals were deposited from the solution. When addition of the nickel carbonyl was complete, the mixture was refluxed for a further 30 minutes, cooled, and filtered. Dicarbonyldi(triphenylphosphino)nickel (13·9 g.) was obtained as a pale cream-coloured crystalline solid, m. p. 210—215° (decomp.) when plunged into a bath preheated to 210° (Reppe and Schweckendiek, *loc. cit.*, gave m. p. 206—209°) (Found: C, 70·7; H, 5·0; Ni, 8·5. Calc. for $C_{38}H_{30}O_2P_2Ni$: C, 71·3; H, 4·7; Ni, 9·2%).

s-*Tri-(α-hydroxybenzyl)benzene*.—Phenylethynylcarbinol (1-phenylpropargyl alcohol) (10 g.) and the catalyst (0·5 g.) were refluxed in methyl alcohol (10 c.c.) overnight; there was no exothermic reaction. Evaporation of the solution, finally at 100°/16 mm., gave a brown gum which slowly crystallised; trituration with ether gave a cream-coloured solid (1·6 g.), m. p. 169—173°, which after repeated crystallisation from benzene afforded 1 : 3 : *5-tri-(α-hydroxybenzyl)benzene*, m. p. 181° (Found: C, 81·3; H, 6·2. $C_{27}H_{24}O_3$ requires C, 81·8; H, 6·1%)

s-*Tribenzoylbenzene*.—The above trimer (0·35 g.) in acetone (5 c.c.) was oxidised by dropwise addition of chromium trioxide (0·2 g.) in water (0·6 c.c.) containing sulphuric acid (0·2 g.). The temperature rose spontaneously to 40°, and after 30 minutes' stirring water was added and the precipitated solid was collected (0·32 g.; m. p. 113—115°). One recrystallisation from alcohol afforded *s*-tribenzoylbenzene, m. p. 117°, undepressed by admixture with an authentic specimen, m. p. 116—118° (Found: C, 83·1; H, 4·2. Calc. for $C_{27}H_{18}O_3$: C, 83·1; H, 4·6%).

1 : 2 : *4-Triphenylbenzene. Polymerisation of Phenylacetylene*.—Phenylacetylene (10 g.) in alcohol (100 c.c.) was heated under reflux on the steam-bath with the catalyst (0·5 g.). At 70° (internal temperature) a violent reaction occurred which was checked by cooling; when this had subsided the mixture was boiled under reflux for 1 hour, a dark oil separating. The mixture was poured into water and the oil extracted with ether, dried, and distilled. Fractions (*a*), b. p. about 160°/0·15 mm., and (*b*), b. p. about 190°/0·15 mm., were collected. Fraction (*a*) solidified and after 3 recrystallisations from alcohol afforded 1 : 2 : *4-triphenylbenzene* as colourless prisms, m. p. 109° (Found: C, 94·25; H, 5·85; *M*, cryoscopic in benzene, 303. $C_{24}H_{18}$ requires C, 94·1; H, 5·9%; *M*, 306). Fraction (*b*), an orange viscous oil, deposited some crystalline material on cooling. It was dissolved in alcohol and cooled, and the mother-liquor decanted. Spontaneous evaporation of the liquor gave a yellow amorphous solid which on repeated recrystallisation from alcohol, and finally from light petroleum, gave white crystals, m. p. 109°, identical with those from fraction (*a*).

3 : 6-endo*Keto*-1 : 2 : *4-triphenyl*cyclo*hex*-1-*ene*.—4-Hydroxy-3 : 4-diphenyl*cyclo*pent-2-en-1-one ("anhydromonoacetone benzil") (10 g.; Japp and Miller, *loc. cit.*), potassium hydrogen sulphate (10 g.), and styrene (20 g.) were refluxed for 2·5 hours. The hot supernatant styrene solution was decanted from the cake of potassium hydrogen sulphate, cooled, and diluted with ether. A pale yellow solid (5·25 g.), m. p. 183—184°, separated. Recrystallisation from alcohol–acetone gave white needles of 3 : 6-endo-*keto*-1 : 2 : *4-triphenyl*cyclo*hex*-1-*ene*, m. p. 188° with effervescence (Found: C, 89·2; H, 5·95. $C_{25}H_{20}O$ requires C, 89·3; H, 5·95%).

When heated at 220—230°, 3 : 6-*endo*keto-1 : 2 : 4-triphenyl*cyclo*hex-1-ene (5 g.) evolved carbon monoxide briskly. The resulting yellow gum could not be induced to crystallise, and was mixed with powdered sulphur (1 g.) and heated at 250° for 4 hours. The product was distilled (b. p. about 170°/0·1 mm.) giving an orange viscous oil, which was dissolved in light petroleum (b. p. 60—80°) and set aside. After 3 days clusters of crystals separated; these were recrystallised twice from light petroleum, sublimed at 100°/0·1 mm., and finally recrystallised, giving white crystals of 1 : 2 : 4-triphenylbenzene, m. p. 109°, undepressed by admixture with material obtained from the polymerisation of penylacetylene.

The authors are indebted to their colleague, Mr. H. P. W. Huggill, for the suggestion for the synthesis of the triphenylbenzene.

IMPERIAL CHEMICAL INDUSTRIES LTD., RESEARCH LABORATORIES,
HEXAGON HOUSE, MANCHESTER, 9.

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17. *The Constituents of Natural Phenolic Resins. Part XXII. Reduction of Some Lactonic Lignans with Lithium Aluminium Hydride.*

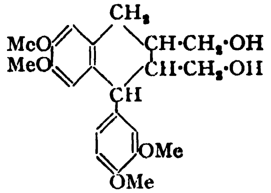
By Robert D. Haworth and Leslie Wilson.

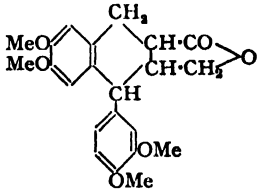
The "trans-"configuration previously assigned to (—)-matairesinol and (—)-hinokinin has been confirmed by reduction with lithium aluminium hydride to optically active diols; (+)-*iso*matairesinol has a "cis-"configuration and gives a *meso*diol on reduction. (—)-Conidendrin dimethyl ether has been reduced to (+)-*iso*lariciresinol dimethyl ether.

The introduction of lithium aluminium hydride as a reagent for the conversion of lactones into diols (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738) suggested several applications in the lignan field, and the present communication describes a number of stereochemical relations which have been established or confirmed by the use of this reagent.

The conversion of (+)-*iso*lariciresinol dimethyl ether (I) into (—)-conidendrin dimethyl ether (II) was reported in an earlier paper (*J.*, 1937, 384), and the reverse change has now been realised by the use of lithium aluminium hydride in ether–benzene, thereby confirming the close stereochemical relation of the two lignans.

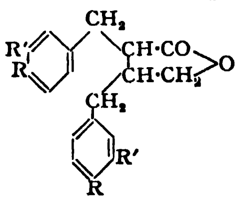
(I.)



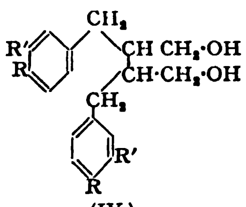


(II.)

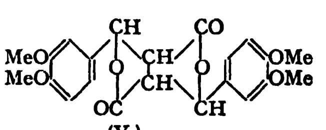
In earlier communications (*J.*, 1938, 797, 1985; 1939, 154, 1054; 1940, 1098), evidence was brought forward suggesting that (—)-matairesinol (III; R = OH, R′ = OMe) has a "trans-" configuration, and the corresponding "cis-"arrangement was assigned to (+)-*iso*matairesinol. These conclusions have now been confirmed by the reduction of (—)-matairesinol dimethyl ether (III; R = R′ = OMe) and (+)-*iso*matairesinol dimethyl ether into the (—) and *meso*-forms of 1 : 4-*di*-(3 : 4-*dimethoxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane* (IV; R = R′ = OMe), respectively. In the same way (—)-hinokinin (III; RR′ = CH_2O_2) has been reduced to (—)-1 : 4-*di*-(3 : 4-*methylenedioxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane* (IV; RR′ = CH_2O_2), identical with "dihydrocubebin" (Bruchhausen and Gerhard, *Ber.*, 1939, **72**, 830), thus confirming the "trans-"configuration previously advanced for (—)-hinokinin.



(III.)



(IV.)



(V.)

Several attempts to reduce the synthetic dilactone (V) (*J.*, 1944, 535) have been made; so far we have failed to isolate crystalline material, but this synthetical route to pinoresinol dimethyl ether is still under investigation.

Experimental.

(+)-iso*Lariciresinol Dimethyl Ether* (I).—Cold solutions of (—)-conidendrin dimethyl ether (1 g.) in benzene (40 c.c.) and of lithium aluminium hydride (0·5 g.) in ether (40 c.c.) were mixed and allowed to react for 2 hours, during which a white gelatinous precipitate separated. The bulk of the solvent was reduced to about 40 c.c. by distillation under reduced pressure, and the precipitated metal alkoxide decomposed by careful addition of dilute hydrochloric acid. The benzene layer was washed twice with water, dried ($CaCl_2$), and evaporated to dryness. The product (0·85 g.) separated from aqueous methyl alcohol in colourless needles, m. p. 167—168°, $[\alpha]_D^{20}$ + 18° (*c*, 1·8272 in chloroform) (cf. *J.*, 1937, 384; m. p. 166—167°, $[\alpha]_D^{14}$ + 20° in chloroform). Anhydro*iso*lariciresinol dimethyl ether, obtained by heating the above diol (I) (0·2 g.) with potassium hydrogen sulphate (0·4 g.) at 180° for ½ hour, crystallised from methyl alcohol in colourless prisms (0·13 g.), m. p. 147—148°, $[\alpha]_D^{23}$ — 33·9° (*c*, 0·3840 in acetone) (cf. *J.*, 1937, 384; m. p. 146—147°, $[\alpha]_D^{16}$ — 33·4° in acetone).

(—)-1 : 4-*Di*-(3 : 4-*dimethoxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane* (IV; R = R′ = OMe).—(—)-Matairesinol dimethyl ether (1 g.) in benzene (30 c.c.) and lithium aluminium hydride (0·5 g.) in ether (30 c.c.) were allowed to react for 2 hours. The volume of the solvent was reduced by distillation, dilute hydrochloric acid was added, and the product from the washed and dried benzene layer was crystallised from methyl alcohol containing a little ether in colourless prisms (0·88 g.), m. p. 119—120°, $[\alpha]_D^{20}$ — 29·6° (*c*, 0·4380 in chloroform) (cf. *J.*, 1939, 1054; m. p. 121—122°, $[\alpha]_D^{17}$ — 26·2° in chloroform). (—)-3 : 4-Di-(3 : 4-dimethoxybenzyl)tetrahydrofuran, obtained by heating the above diol (0·15 g.) with potassium hydrogen sulphate (0·3 g.) at 180° for ½ hour, separated from methyl alcohol in colourless prisms (0·11 g.), m. p. 117—118°, $[\alpha]_D^{25}$ — 54·5° (*c*, 0·0928 in chloroform) (cf. *J.*, 1939, 1054; m. p. 118—119°, $[\alpha]_D^{17}$ — 58·9° in chloroform).

meso-1 : 4-*Di*-(3 : 4-*dimethoxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane*.—(+)-iso*Matairesinol* dimethyl ether (0·1 g.) in benzene (5 c.c.) was treated with cold lithium aluminium hydride (0·05 g.) in ether (5 c.c.). After 2 hours the volume was reduced by distillation under reduced pressure, and dilute hydrochloric acid was added. The product, isolated from the benzene layer, crystallised from methyl alcohol in colourless prisms (0·079 g.), m. p. 94—95°, [α] 0° (*c*, 0·1861 in chloroform) (Found : C, 67·5; H, 7·5. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7%).

meso-3 : 4-*Di*-(3 : 4-*dimethoxybenzyl*)*tetrahydrofuran*, obtained by heating the *meso*-diol (0·06 g.) with potassium hydrogen sulphate (0·12 g.) at 180° for 0·5 hours, separated from methyl alcohol in colourless prisms (0·05 g.), m. p. 114—115°, [α] 0° (*c*, 0·0884 in chloroform) (Found : C, 70·8; H, 7·7. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·6%).

(—)-1 : 4-*Di*-(3 : 4-*methylenedioxyphenyl*)-2 : 3-*di*(*hydroxymethyl*)*butane* (IV; RR′ = CH_2O_2).—(—)-Hinokinin (1 g.) in benzene (50 c.c.) was mixed with a solution of lithium aluminium hydride (0·5 g.) in ether (50 c.c.). After 2 hours, dilute hydrochloric acid was added, and the diol, isolated from the benzene layer, separated from ether–light petroleum (b. p. 60—90°) in colourless needles (0·93 g.), m. p. 102—103°, $[\alpha]_D^{20}$ — 34° (*c*, 0·8476 in chloroform) (Bruchhausen and Gerhard, *loc. cit.*, give m. p. 104°, $[\alpha]_D^{18}$ — 30·6° in chloroform). (—)-3 : 4-*Di*-(3 : 4-*methylenedioxybenzyl*)*tetrahydrofuran*, formed by heating the above diol (0·2 g.) with potassium hydrogen sulphate (0·4 g.) at 180° for ½ hour, was distilled at 0·5 mm. (bath temperature, 280—300°) and crystallised from ether–light petroleum (b. p. 60—90°) in colourless prisms (0·14 g.), m. p. 52—52·5° $[\alpha]_D^{22}$ — 58·3° (*c*, 0·1716 in chloroform) (Found : C, 70·6; H, 6·2. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

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THE UNIVERSITY, SHEFFIELD, 10.

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18. *Experiments with Diazomethane and its Derivatives. Part XV. Action of Diazomethane on* o-*Quinone Monoximes.*

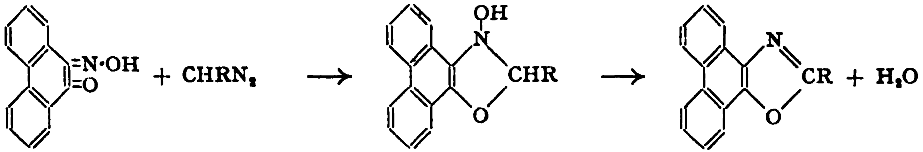
By ALEXANDER SCHÖNBERG and WILLIAM IBRAHIM AWAD.

Reaction of the monoximes of phenanthraquinone, retenequinone, and chrysenequinone with diazomethane or diazoethane leads to oxazole derivatives. Oxazoline derivatives corresponding to the intermediate (I) were found in the case of acenaphthenequinone monoxime, triketoindane-2 oxime, and 2-oximino-3 : 3-diphenylindan-1-one.

A scheme is advanced showing the similarity of the action of diazomethane on diketones, *o*-quinones, *a*-keto-lactones, *o*-quinone imines and monoximes, ketomethylene derivatives, and thiourea.

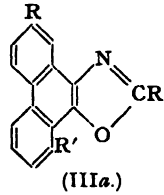
VERY little is known about the action of diazomethane on *o*-quinone monoximes. It is stated, however, that oximinocamphor (stable or unstable form) gives, with diazomethane, the *N*-methyl ether (Forster and Holmes, *J.*, 1908, **93**, 247).

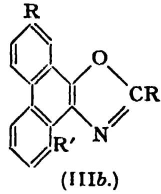
When phenanthraquinone monoxime was treated with diazomethane, phenanthroxazole (II*a*) was obtained by loss of water from an intermediate product (I), which was not isolated. The action of diazoethane led to 2-methylphenanthroxazole (II*b*).

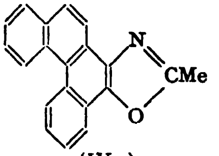


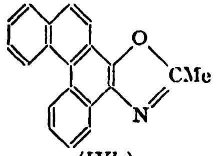
(I.) (II*a*; R = H.) (II*b*; R = Me.)

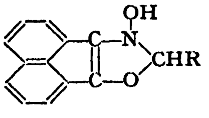
Diazomethane with retenequinone monoxime yielded reteno-oxazole (III*a* or *b*; R = Me, R′ = Pr^i, R″ = H), the uncertainty being caused by lack of knowledge of the position of the oximino-group present in retenequinone monoxime. Diazoethane similarly yields 2-methylreteno-oxazole (III*a* or *b*; R = Me, R′ = Pr^i, R″ = Me). The products (III) are identical with those previously obtained from retenequinone imine. Schönberg and Awad (*J.*, 1947, 651) pointed out the uncertainty concerning the structure of reteno-oxazoles, but defined it incorrectly in formulæ (II)—(IV) of that paper.

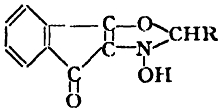

(III*a*.)

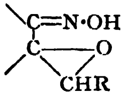

(III*b*.)

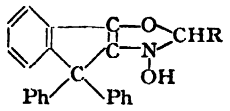

(IV*a*.)


(IV*b*.)


(V*a*; R = H.)
(V*b*; R = Me.)

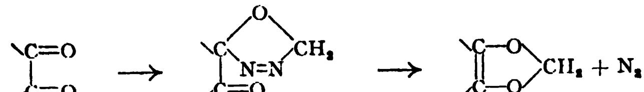

(VI*a*; R = H.)
(VI*b*; R = Me.)

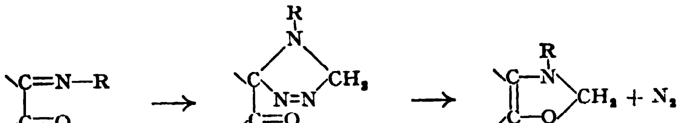

(VII.)

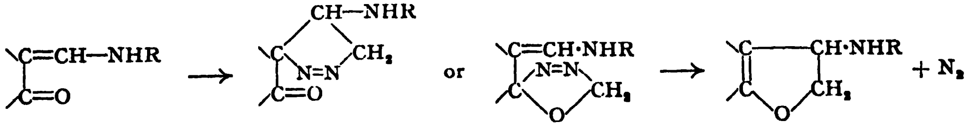

(VIII*a*; R = H.)
(VIII*b*; R = Me.)

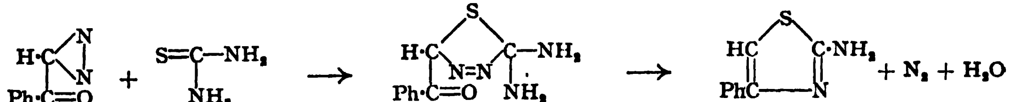
Diazoethane and chrysenequinone monoxime similarly give the 2-methylchryseno-oxazole (IV*a* or *b*).

Diazomethane and acenaphthenequinone monoxime or triketoindane-2 oxime give 3-*hydroxy-acenaphthyleno*(7′ : 8′-4 : 5)*oxazoline* (V*a*) or 3-*hydroxy*-1′-*ketoindeno*(2′ : 3′-4 : 5)*oxazoline* (VI*a*). (V*a*) and (VI*a*) are pale yellow substances. They contain no methoxy-group and only one active hydrogen atom (Zeisel's method). Acid hydrolysis of (V*a*) gives acenaphthenequinone, probably owing to the oxidation of the intermediate 1 : 2-dihydroxyacenaphthylene. (VI*a*) similarly yields triketoindane hydrate (ninhydrin). The results of hydrolysis make it improbable that the heterocyclic rings in (V*a*) and (VI*a*) can be replaced by (VII), since such substances are not expected to be hydrolysed in acid to acenaphthenequinone and triketoindane which would necessitate the rupture of a C–C linkage. According to Wanag and Lode (*Ber.*, 1939, **72**, 49) triketoindane 2-oxime is to be formulated as 2-nitrosoindane-1 : 3-dione but in our opinion its pale yellow colour is not in agreement with this hypothesis. (V*b*) and (VI*b*) were obtained by use of diazoethane.


(IX*a*.) (IX*b*.) (IX*c*.)

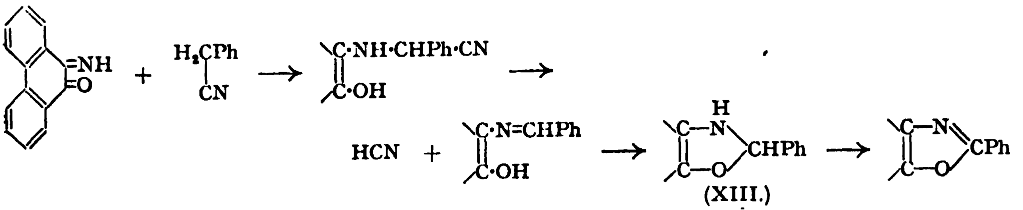

(X*a*.) (X*b*.) (X*c*.)


(XI*a*.) (XI*b*.) (XI*c*.) (XI*d*.)


(XII*a*.) (XII*b*.) (XII*c*.)

The action of diazomethane on 2-oximino-3 : 3-diphenylindan-1-one yielded **3-*hydroxy*-1′ : 1′-*diphenylindeno*(2′ : 3′-4 : 5)*oxazoline*** (VIII*a*), a pale yellow substance containing one active hydrogen atom; with diazoethane the 2-*methyl* derivative (VIII*b*) was obtained.

The formation of five-membered ring compounds by the action of diazomethane and its derivatives on 1 : 2-diketones, *o*-quinones, α-keto-lactones (cf. IX*a* ⟶ IX*c*), *o*-quinone imines and monoximes (cf. X*a* ⟶ X*c*; R = H or OH), ketomethylene derivatives (cf. XI*a* ⟶ XI*d*), and thiourea (cf. XII*a* ⟶ XII*c*) may all be regarded as proceeding according to the same scheme, *i.e.*, addition of diazomethane to the >C=O, >C=N—, >C=C<, or >C=S group (cf. IX*b* and XI*c*, X*b*, XI*b*, and XII*b*), followed by the elimination of nitrogen.


(XIII.)

For the action of diazomethane on 1 : 2-diketones, *o*-quinones, coumarandiones, and thiocoumarandiones see Biltz and Paetzold (*Annalen*, 1923, **433**, 71), Arndt, Amende, and Ender (*Monatsh.*, 1932, **59**, 202), Fieser and Hartwell (*J. Amer. Chem. Soc.*, 1935, **57**, 1479), and Schönberg, Moubasher, and Mostafa (*J.*, 1941, 348). For the action on quinone imines (X*a*; R = H) see Schönberg and Awad (*loc. cit.*); the products actually obtained (*e.g.*, II*a* in the case of phenanthraquinone-imine and diazomethane) are oxazole derivatives formed by dehydrogenation of the intermediate products (*e.g.*, XIII, but with H replacing Ph). Reaction (X*a* ⟶ X*c*; R = OH) is described in this paper. For (XI*a* ⟶ XI*d*) see Schönberg, Mustafa, and Hilmy (*J.*, 1947, 1946). For the formation of (XII*c*) see King and Miller (*J. Amer. Chem. Soc.*, 1949, 367), who however do not discuss the formation of (XII*b*).

In connection with the synthesis of the phenanthroxazole derivatives, we have obtained 2-phenylphenanthroxazole (II, R = Ph) by the action of benzyl cyanide or deoxybenzoin on phenanthraquinone imine. In the case of benzyl cyanide the reaction is believed to proceed according to to the scheme above, and a similar one is proposed for the action of deoxybenzoin. The dehydrogenation required in the last step may be due to the oxidation by atmospheric oxygen or a second molecule of phenanthraquinone imine (Schönberg and Awad, *loc. cit.*). The action of *p*-nitrobenzyl cyanide leads to the formation of 2-*p*-nitrophenylphenanthroxazole.

EXPERIMENTAL.

The ethereal solution of diazomethane (diazoethane) was prepared according to *Org. Synth.*, Vol. 15, p. 3 (Werner, *J.*, 1919, **115**, 1093).

Action of Diazomethane on Oximes.—(a) *Phenanthraquinone monoxime* (Goldschmidt, *Ber.*, 1883, **16**, 2178). The oxime (0·5 g.) was suspended in ether and treated with an excess of ethereal diazomethane as usual for 6 hours. The solution was evaporated to dryness *in vacuo*, and the residue recrystallised from methyl alcohol; phenanthroxazole (II*a*) was obtained in light-yellow crystals, m. p. 152° (Found : C, 81·8; H, 4·0; N, 6·4. Calc. for $C_{15}H_9ON$: C, 82·2; H, 4·1; N, 6·4%). A mixed-m. p. determination with phenanthroxazole prepared according to Schönberg and Awad (*loc. cit.*) gave no depression; both samples gave the same colour with concentrated sulphuric acid.

(b) *Retenequinone monoxime* (Bamberger and Hooker, *Annalen*, 1885, **229**, 102). Reteno-oxazole (III*a* or III*b*; R = Me, R′ = Pr^{i}, R″ = H) recrystallised from methyl alcohol in yellow crystals, m. p. 108°, undepressed on admixture with an authentic specimen (Schönberg and Awad, *loc. cit.*) (Found : C, 82·7; H, 6·1; N, 5·2. Calc. for $C_{19}H_{17}ON$: C, 82·9; H, 6·2; N, 5·1%).

(c) *Acenaphthenequinone monoxime* (Francesconi and Pirazzoli, *Gazzetta*, 1903, **33**, I, 36). 3-*Hydroxyacenaphthyleno*(7′ : 8′-4 : 5)*oxazoline* (V*a*) recrystallised from methyl alcohol in yellow crystals, m. p. 163°. It gives a yellowish-orange colour in concentrated sulphuric acid, is insoluble in concentrated aqueous sodium hydroxide solution, and sublimes *in vacuo* (boiling ethyl cinnamate bath) (Found : C, 73·4; H, 4·3; N, 6·8; active H, 0·58; OMe, nil. $C_{13}H_9O_2N$ requires C, 73·9; H, 4·3; N, 6·6; one active H, 0·47%).

(d) 2-*Oximino*-3 : 3-*diphenylindan*-1-*one* (Koelsch and Le Claire, *J. Org. Chem.*, 1941, **6**, 531). 3-*Hydroxy*-1′ : 1′-*diphenylindeno*(2′ : 3′-4 : 5)*oxazoline* (VIII*a*) recrystallised from methyl alcohol in light-yellow crystals, m. p. 178° (Found : C, 80·0; H, 5·1; N, 4·5; active H, 0·3. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3; one active H, 0·3%). It gave a yellowish-orange colour in concentrated sulphuric acid.

(e) *Triketoindane* 2-*oxime* (Teeters and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 3026). 3-*Hydroxy*-1′-*ketoindeno*(2′ : 3′-4 : 5)*oxazoline* (VI*a*) was obtained in a way similar to that described previously, but ½ hour after the addition of the diazomethane solution a green deposit was formed which was filtered off. After recrystallisation twice from ethyl alcohol (96%) and then from methyl alcohol, yellow crystals of (VI*a*) were obtained, having m. p. 247° (to a reddish-brown melt; shrinking before melting) (Found: C, 63·4; H, 4·0; N, 7·87; OMe, nil. $C_{10}H_7O_3N$ requires C, 63·5; H, 3·7; N, 7·4%). It gave a yellowish-orange colour with concentrated sulphuric acid.

Hydrolysis of 3-Hydroxyacenaphthyleno-oxazoline.—The substance (0·2 g.) was dissolved in hot methyl alcohol (10 c.c.), and then concentrated hydrochloric acid (10 c.c.) was added. The mixture was refluxed for 2 hours and left to cool; the brown precipitate recrystallised from glacial acetic acid in yellow crystals which proved to be acenaphthenequinone, the m. p. being undepressed on admixture with an authentic specimen; both samples gave the same colour with concentrated sulphuric acid.

Hydrolysis of (VI*a*).—The substance (VI*a*) (0·1 g.) was dissolved in glacial acetic acid (15 c.c.), and an equal volume of concentrated hydrochloric acid was added. The mixture was refluxed for 4 hours. The solution was evaporated under normal pressure till a solid began to appear, and then cooled and filtered. The product was impure ninhydrin, as it gave a violet colour on the skin in the presence of water. The substance when treated with concentrated sodium hydroxide solution gave the blue colour reaction of ninhydrin.

Action of Diazoethane on Oximes.—(a) *Phenanthraquinone monoxime.* The oily residue obtained after the ether had been distilled off was cooled and scratched, with a little dilute methyl alcohol; it solidified to a brownish amorphous mass, which crystallised from methyl alcohol in light-yellow crystals, m. p. 145°, undepressed on admixture with an authentic specimen of 2-methylphenanthroxazole (II*b*), prepared according to Schönberg and Awad (*loc. cit.*) (Found: C, 82·6; H, 4·8; N, 5·7. Calc. for $C_{16}H_{11}ON$: C, 82·4; H, 4·7; N, 6·0%).

(b) *Retenequinone monoxime.* 2-Methylreteno-oxazole (III; R = Me, R′ = Pr^i, R″ = Me) recrystallised from dilute methyl alcohol (80%) in light-yellow crystals, m. p. 135°, undepressed on admixture with an authentic specimen prepared according to Schönberg and Awad (*loc. cit.*) (Found: C, 83·4; H, 6·7; N, 4·7. Calc. for $C_{20}H_{19}ON$: C, 83·0; H, 6·6; N, 4·8%).

(c) *Chrysenequinone monoxime* (Graebe and Hönigsberger, *Annalen*, 1900, **311**, 272). 2-*Methylchryseneoxazole* (IV*a* or *b*) recrystallised from methyl alcohol in yellow crystals, m. p. *ca.* 223° (Found: C, 84·9; H, 4·9; N, 4·5. $C_{20}H_{13}ON$ requires C, 84·8; H, 4·6; N, 4·9%).

(d) *Acenaphthenequinone monoxime.* 3-*Hydroxy-2-methylacenaphthylene*(7′ : 8′-4 : 5)*oxazoline* (V*b*) recrystallised from methyl alcohol in yellow crystals, m. p. 93°, and gave an orange colour in concentrated sulphuric acid (Found: N, 6·4; active H, 0·48. $C_{14}H_{11}O_2N$ requires N, 6·2; one active H, 0·44%).

(e) 2-*Oximino*-3 : 3-*diphenylindan*-1-*one.* 3-*Hydroxy*-1′ : 1′-*diphenyl-2-methylindeno*(2′ : 3′-4 : 5)-*oxazoline* (VIII*b*) crystallised from methyl alcohol in yellow crystals, m. p. 152° (Found: C, 80·7; H, 5·6; N, 3·9. $C_{23}H_{19}O_2N$ requires C, 80·9; H, 5·6; N, 4·1%). It gave an orange colour with concentrated sulphuric acid.

(f) *Triketoindane 2-oxime.* 3-*Hydroxy*-1′-*keto-2-methylindeno*(2′ : 3′-4 : 5)*oxazoline* (VI*b*) crystallised from methyl alcohol in yellow crystals, m. p. 160°, insoluble in cold sodium hydroxide solution (Found: C, 64·9; H, 4·5. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4%).

Action of (a) *Benzyl Cyanide,* (b) *Deoxybenzoin, and* (c) p-*Nitrobenzyl Cyanide on Phenanthraquinone Imine.*—(a) The imine (0·5 g.) and benzyl cyanide (0·3 g.) in anisole (5 c.c.) were refluxed for 1 hour, after which the anisole was evaporated off. The residual brown oil was cooled in an ice–salt mixture and triturated with alcohol (98%) at that temperature, whereby a yellow solid was formed. The product (II; R = Ph), crystallised from ethyl alcohol, had m. p. 202°, undepressed on admixture with an authentic specimen of 2-phenylphenanthroxazole prepared according to Stein and Day (*J. Amer. Chem. Soc.*, 1942, **64**, 2567) (Found: C, 85·1; H, 4·5; N, 4·6. Calc. for $C_{21}H_{13}ON$: C, 85·4; H, 4·4; N, 4·8%).

(b) The reaction was carried out as above, and the 2-phenylphenanthroxazole produced, after crystallisation from ethyl alcohol, had m. p. 202°, undepressed on admixture with the product obtained in (a) (Found: C, 85·4; H, 4·8; N, 4·8%).

(c) p-*Nitrobenzyl cyanide.* The reaction was carried out as in (a) with the imine (0·5 g.) and *p*-nitrobenzyl cyanide (0·5 g.). 2-*p*-Nitrophenylphenanthroxazole (II; R = *p*-NO_2·C_6H_4) obtained on cooling the mixture was crystallised from chloroform as yellow crystals, m. p. 268° (Found: C, 74·1; H, 3·6; N, 7·8. Calc. for $C_{21}H_{12}O_3N_2$: C, 74·3; H, 3·5; N, 8·2%). Schiedt (*J. pr. Chem.*, 1941, **157**, 203) gives m. p. 272°.

Fouad I University, Abbassia, Cairo.

[*Received, June 2nd,* 1949.]

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19. *The Physical Properties of Some Aliphatic Compounds.*

By S. A. Mumford and J. W. C. Phillips.

Measurements are reported of the densities, refractive indices, surface tensions, and viscosities, at 20° and 25° whenever practicable, of a number of aliphatic compounds of different types.

The results are briefly discussed from the standpoint of the parachor thesis previously advanced (*J.*, 1929, 2112).

In the decade following publication of a paper on the evaluation and interpretation of parachors (*J.*, 1929, 2112) the authors undertook, as opportunity arose, the determination of the surface tension and other physical properties of a number of aliphatic compounds, with the object of obtaining further evidence in support of the thesis then advanced, namely that the CH_2 parachor increment of 39 units originally adopted by Sugden (*J.*, 1924, **125**, 1177) was too small and should be replaced by one of 40 units, and that constitutive deviations from parachor additivity could be accounted for by the systematic introduction of " strain constants." The investigation was interrupted by the war, and as circumstances have since arisen which make it impossible to resume the collaboration, it has been thought desirable to place on record the results obtained up to 1939.

The original aim of the investigation was twofold : (i) to obtain a representative value for the CH_2 increment by examining the average parachor increase over a considerable CH_2 interval in a number of different aliphatic series; and (ii) to obtain more detailed information on the magnitude of the parachor defect associated with accumulation of negative groups in a molecule, particularly on one carbon atom. With the first object in view, a series of *n*-hexadecyl compounds was prepared, and their parachors, determined at uniform temperature as far as practicable, were compared with those of the corresponding *n*-butyl derivatives. Later, examination was made of a number of intermediate members in some of the series, to check the atomic or group constants concerned. The second aim of the investigation involved measurement of the parachors of a number of polyhalogenated hydrocarbons, ethers, and sulphides, and of a series of alkyl mono-, di-, and tri-chloroacetates, and αω-dihalogeno- and -di-carbethoxy-alkanes.

EXPERIMENTAL.

Many of the compounds were purified from commercially available materials (generally from Messrs. British Drug Houses or Schering-Kahlbaum). As regards the others, the methods of preparation employed were those in general use. Thus, the *n*-alkyl halides were prepared from the corresponding purified alcohols by treatment with the requisite phosphorus halide. (In the case of the *n*-amyl compounds, the alcohol was synthesised from purified *n*-butyl bromide, which was also the starting point for the preparation of synthetic *n*-valeric acid.) The chlorinated esters were obtained by esterification of the appropriate acid with the requisite purified alcohol, and the alkyl 2-chloroethyl ethers by the action of methyl or ethyl sulphate on ethylene chlorohydrin. 2 : 2′-Dichlorodiethyl ether was prepared in a manner analogous to that used by Kamm and Waldo (*J. Amer. Chem. Soc.*, 1921, **43**, 2223), and penta-chlorodiethyl ether by treating the condensation product of chloral and ethylene chlorohydrin with phosphorus pentachloride (Henry, *Ber.*, 1874, **7**, 763). Tetra- and penta-methylene dichloride were prepared from adipamide and piperidine, respectively, by the method of von Braun (*Ber.*, 1905, **38**, 2340; 1906, **39**, 4119). The *n*-alkyl sulphides were obtained by the action of sodium sulphide on the appropriate alkyl bromide, and 2-chlorodiethyl sulphide by the action of thionyl chloride on the condensation product of sodium thioethoxide and ethylene chlorohydrin (Mayer, *Annalen*, 1877, **240**, 310). All the products were purified to constant properties by repeated fractionation through a Young column. The preparation of the *n*-hexadecyl compounds and of the polychlorinated sulphides has already been reported (*J.*, 1931, 1732; 1929, 535). See also *Rec. Trav. chim.*, 1933, **52**, 175, 181, and *J.*, 1934, 1657 for the preparation of the higher ethyl esters, alcohols, and acetates.

Refractive indices were measured, at 20° whenever possible, with a calibrated Abbé refractometer. The other physical properties were determined at two temperatures (20° and 25° where practicable), the values quoted being the means of at least two determinations, made with different apparatus, at each temperature. The densities were determined with water-calibrated specific-gravity bottles, all weighings being reduced to a vacuum; the surface tensions were measured by Sugden's modification of the maximum bubble-pressure method (*J.*, 1922, **121**, 860), using bubblers calibrated with pure benzene (f.p. 5·5°, b. p. 80·2°, d_4^{20} 0·8790, n_D^{20} 1·5012), taking $\gamma_{20} = 28{\cdot}88$ dynes/cm.; the viscosities were determined in small Ostwald-type viscometers conforming in general characteristics to the standards laid down in British Standard Specification No. 188—1929, and calibrated with water and/or standard sugar solutions.

RESULTS.

Compound.	F. p.	B. p. (760 mm. except where stated).	t.	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
2 : 5-Dimethylhexane	—	109·2°	20°	0·6994	1·3933	38·98	19·9	344·7	0·485
			25	0·6959	—	—	19·4	344·2	0·456
n-Decane	—	173·3	20	0·7307	1·4116	48·37	24·0	430·8	0·920
			25	0·7270	—	—	23·5	430·6	0·855
n-Hexadecane	17·6°	285·8	20	0·7746	1·4350	76·22	27·8	670·7	3·53
			25	0·7712	—	—	27·35	670·9	3·10
n-Hexadec-1-ene	—	159·5	20	0·7825	1·4428	75·95	27·9	658·7	3·09
		(21 mm.)	25	0·7792	—	—	27·45	658·8	2·76
n-Propyl chloride	—	46·5	20	0·8890	1·3900	20·94	22·15	191·6	0·355
			25	0·8830	—	—	21·5	191·5	0·337
n-Butyl chloride	—	78·4	20	0·8866	1·4021	25·42	23·75	230·4	0·450
			25	0·8811	—	—	23·1	230·2	0·427
*iso*Butyl chloride	—	68·4	20	0·8780	1·3978	25·42	21·95	228·1	0·457
			25	0·8725	—	—	21·4	228·1	0·431

RESULTS (*continued*).

Compound.	F. p.	B. p (760 mm. except where stated).	t.	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
n-Amyl chloride	—	107·9°	20°	0·8840	1·4125	30·02	25·15	269·9	0·580
			25	0·8795	—	—	24·55	269·7	0·547
tert.-Amyl chloride	—	85·6	20	0·8659	1·4050	30·16	22·3	267·4	0·599
			25	0·8612	—	—	21·8	267·3	0·560
n-Hexyl chloride	—	134·3	20	0·8790	1·4195	34·67	26·15	310·2	0·743
			25	0·8745	—	—	25·55	310·0	0·696
n-Heptyl chloride	—	160·0	20	0·8759	1·4255	39·33	26·9	349·9	0·956
			25	0·8715	—	—	26·35	349·9	0·890
n-Octyl chloride	—	183·8	20	0·8735	1·4298	43·93	27·65	390·1	1·23
			25	0·8695	—	—	27·15	390·1	1·135
sec.-Octyl chloride	—	171·9	20	0·8660	1·4283	44·17	26·4	388·9	1·055
			25	0·8616	—	—	25·9	389·1	0·973
n-Hexadecyl chloride	α 7·4°	195	20	0·8649	1·4495	80·93	31·1	711·8	6·34
	β 12·1	(22·5 mm.)	25	0·8616	—	—	30·6	711·7	5·51
Allyl chloride	—	45·0	20	0·9349	1·4165	20·56	23·7	180·5	0·347
			25	0·9290	—	—	23·1	180·5	0·331
Chlorobenzene	—	131·3	20	1·1065	1·5246	31·14	33·25	244·1	0·801
			25	1·1013	—	—	32·65	244·1	0·756
Benzyl chloride	—	67	20	1·0993	1·5391	36·06	37·65	285·1	1·40
		(14 mm.)	25	1·0945	—	—	36·95	285·0	1·29
Ethyl bromide	—	38·2	20	1·4612	1·4242	19·04	24·1	165·2	0·397
			25	1·4515	—	—	23·45	165·2	0·379
*iso*Propyl bromide	—	59·4	20	1·3096	1·4251	24·02	23·1	205·9	0·487
			25	1·3017	—	—	22·5	205·9	0·463
n-Butyl bromide	—	101·5	20	1·2758	1·4397	28·28	26·6	243·9	0·633
			25	1·2687	—	—	26·0	243·8	0·597
*iso*Butyl bromide	—	91·1	20	1·2641	1·4362	28·34	24·75	241·5	0·637
			25	1·2568	—	—	24·1	241·7	0·601
n-Amyl bromide	—	129·4	20	1·2190	1·4443	32·93	27·35	283·3	0·803
			25	1·2132	—	—	26·8	283·2	0·753
n-Hexyl bromide	—	154·6	20	1·1746	1·4475	37·57	28·2	323·7	1·013
			25	1·1691	—	—	27·65	323·7	0·941
n-Heptyl bromide	—	69·5	20	1·1406	1·4498	42·16	28·6	363·0	1·29
		(17 mm.)	25	1·1352	—	—	28·1	363·1	1·19
n-Octyl bromide	—	202·2	20	1·1126	1·4526	46·86	29·1	403·0	1·64
			25	1·1077	—	—	28·6	403·0	1·50
n-Hexadecyl bromide	16·3	190	20	0·9992	1·4614	83·87	31·8	725·3	7·81
		(11 mm.)	25	0·9952	—	—	31·4	725·3	6·75
Ethyl iodide	—	72·3	20	1·9364	1·5130	24·21	28·85	186·7	0·584
			25	1·9253	—	—	28·2	186·7	0·557
n-Propyl iodide	—	102·5	20	1·7478	1·5051	28·85	29·2	226·1	0·735
			25	1·7385	—	—	28·6	226·1	0·695
n-Butyl iodide	—	130·2	20	1·6150	1·4999	33·50	29·25	264·9	0·877
			25	1·6070	—	—	28·7	265·0	0·826
n-Hexyl iodide	—	76·5	20	1·4391	1·4926	42·79	30·25	345·5	1·39
		(23 mm.)	25	1·4326	—	—	29·75	345·7	1·285
n-Hexadecyl iodide	22·5	184	25	1·1220	1·4795	89·07	32·4	748·9	8·43
		(4 mm.)	30	1·1180	—	—	32·0	749·2	7·27
Methylene chloride	—	39·8	20	1·3283	1·4233	16·29	28·0	147·1	0·437
			25	1·3191	—	—	27·15	147·0	0·416
Chloroform	—	61·2	20	1·4892	1·4458	21·36	27·2	183·1	0·566
			25	1·4798	—	—	26·55	183·2	0·538
Carbon tetrachloride	—	76·75	20	1·5942	1·4603	26·47	26·75	219·5	0·968
			25	1·5846	—	—	26·15	219·6	0·902
1 : 2-Dichloroethane	—	83·6	20	1·2527	1·4448	21·02	32·45	188·5	0·829
			25	1·2454	—	—	31·75	188·6	0·775

Results (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	t.	d_4^t.	n_D.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
1 : 3-Dichloropropane	—	120·8°	20°	1·1859	1·4483	25·52	33·8	229·7	1·034
			25	1·1800	—	—	33·05	229·6	0·963
1 : 4-Dichlorobutane	—	155·0	20	1·1408	1·4549	30·20	34·8	270·4	1·43
			25	1·1353	—	—	34·05	270·2	1·315
1 : 5-Dichloropentane	—	182·0	20	1·1006	1·4566	34·87	35·3	312·3	1·815
			25	1·0956	—	—	34·6	312·1	1·655
Ethylidene dichloride	—	57·3	20	1·1757	1·4167	21·16	24·75	187·7	0·490
			25	1·1680	—	—	24·1	187·7	0·465
1 : 1 : 2-Trichloroethane	—	114·1	20	1·4424	1·4715	25·87	33·75	222·9	1·19
			25	1·4355	—	—	33·0	222·7	1·10
1 : 1 : 2 : 2-Tetrachloroethane	—	146·1	20	1·5953	1·4940	30·62	35·6	256·9	1·765
			25	1·5876	—	—	34·9	256·9	1·615
1 : 1 : 1 : 2 : 2-Pentachloroethane	—	160·5	20	1·6813	1·5030	35·57	34·55	291·7	2·58
			25	1·6740	—	—	33·85	291·5	2·23
1 : 2 : 3-Trichloropropane	—	156·0	20	1·3880	1·4834	30·35	37·8	263·3	2·505
			25	1·3818	—	—	37·05	263·2	2·23
1 : 2-Dichloroethylene, *cis*	—	48·4	20	1·2583	—	—	26·4	174·6	0·423
			25	1·2502	—	—	25·8	174·7	0·400
1 : 2-Dichloroethylene, *trans*	—	60·1	20	1·2841	—	—	28·3	174·1	0·474
			25	1·2771	—	—	27·65	174·0	0·451
Trichloroethylene	—	86·9	20	1·4642	1·4775	25·38	29·5	209·1	0·566
			25	1·4559	—	—	28·8	209·1	0·532
Perchloroethylene	—	121·2	20	1·6230	1·5055	30·33	32·1	243·2	0·891
			25	1·6145	—	—	31·4	243·2	0·842
1 : 2-Dibromoethane	—	131·1	20	2·1802	1·5385	26·98	38·85	215·1	1·73
			25	2·1700	—	—	38·2	215·2	1·60
1 : 3-Dibromopropane	—	166·2	20	1·9812	1·5230	31·13	40·1	256·4	2·07
			25	1·9727	—	—	39·4	256·4	1·90
Ethyl *n*-butyl ether	—	92·0	20	0·7495	1·3820	31·71	20·75	290·8	0·421
			25	0·7448	—	—	20·25	290·8	0·397
Ethyl *n*-hexadecyl ether	19·9°	195 (21 mm.)	20	0·8182	1·4394	86·96	29·4	769·3	6·12
			25	0·8150	—	—	28·95	769·3	5·25
Methyl 2-chloroethyl ether	—	90·3	20	1·0522	1·4108	22·30	29·25	208·9	0·633
			25	1·0461	—	—	28·5	208·7	0·591
2-Chlorodiethyl ether	—	108·4	20	0·9954	1·4118	27·12	27·45	249·6	0·730
			25	0·9894	—	—	26·9	249·8	0·677
1 : 2-Dichlorodiethyl ether	—	51 (27 mm.)	20	1·1670	1·4418	32·40	29·8	286·2	1·285
			25	1·1610	—	—	29·1	286·0	1·165
2 : 2′-Dichlorodiethyl ether	—	177·9	20	1·2192	1·4573	31·95	37·6	290·4	2·41
			25	1·2130	—	—	37·0	290·7	2·14
1 : 2 : 2-Trichlorodiethyl ether	—	62 (13 mm.)	20	1·3227	1·4648	37·07	32·8	321·0	2·46
			25	1·3155	—	—	32·2	321·3	2·18
1 : 2 : 2 : 2 : 2′-Pentachlorodiethyl ether	—	112·5 (12·5 mm.)	20	1·5733	1·5025	46·25	38·9	391·1	9·36
			25	1·5669	—	—	38·3	391·0	7·83
Ethyl formate	—	54·3	20	0·9237	1·3599	17·69	23·8	177·1	0·402
			25	0·9173	—	—	23·15	177·1	0·382
Ethyl acetate	—	77·15	20	0·9007	1·3728	22·26	23·95	216·3	0·452
			25	0·8946	—	—	23·3	216·3	0·425
Ethyl butyrate	—	121·4	20	0·8794	1·3922	31·45	24·6	294·1	0·672
			25	0·8742	—	—	24·0	294·0	0·627
Ethyl valerate	—	145·1	20	0·8750	1·4005	36·09	25·4	333·8	0·821
			25	0·8703	—	—	24·85	333·8	0·763
Ethyl hexoate	—	167·0	20	0·8717	1·4072	40·72	26·0	373·4	1·024
			25	0·8672	—	—	25·45	373·3	0·948
Ethyl octoate	—	207·0	20	0·8676	1·4180	50·01	27·2	453·2	1·58
			25	0·8635	—	—	26·75	453·4	1·44

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t*.	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
Ethyl nonoate	—	119°	20°	0·8661	1·4219	54·61	27·8	493·6	1·95
		(23 mm.)	25	0·8621	—	—	27·35	493·8	1·77
Ethyl laurate	−3·4°	275	20	0·8628	1·4310	68·47	29·05	614·1	3·36
			25	0·8591	—	—	28·6	614·3	2·99
Ethyl myristate	10·85	308·8	20	0·8616	1·4363	77·80	29·9	695·5	4·97
			25	0·8581	—	—	29·45	695·7	4·36
Ethyl palmitate	α 19·2	198·5	25	0·8568	1·4380	87·10	29·95	776·2	5·78
	β 23·2	(13·5 mm.)	30	0·8535	—	—	29·5	776·2	5·08
Ethyl margarate	α 25·2	200	30	0·8517	1·4380	91·94	29·65	817·3	5·815
	Tr↓11·5	(10 mm.)	35	0·8484	—	—	29·2	817·3	5·095
Methyl acetate	—	56·9	20	0·9342	1·3614	17·56	24·8	176·9	0·385
			25	0·9279	—	—	24·1	176·8	0·364
n-Propyl acetate	—	101·6	20	0·8874	1·3844	26·92	24·6	256·2	0·585
			25	0·8822	—	—	24·0	256·2	0·551
n-Butyl acetate	—	125·6	20	0·8796	1·3942	31·58	25·2	295·7	0·734
			25	0·8746	—	—	24·6	295·7	0·688
*iso*Butyl acetate	—	117·1	20	0·8745	1·3898	31·45	23·7	292·9	0·697
			25	0·8695	—	—	23·15	292·9	0·651
n-Amyl acetate	—	149·2	20	0·8753	1·4028	36·26	25·8	335·1	0·924
			25	0·8707	—	—	25·25	335·1	0·862
n-Hexyl acetate	—	170·5	20	0·8726	1·4096	40·89	26·55	374·9	1·17
			25	0·8681	—	—	26·0	374·9	1·075
n-Octyl acetate	—	211·5	20	0·8681	1·4193	50·11	27·8	455·5	1·85
			25	0·8638	—	—	27·3	455·7	1·68
n-Hexadecyl acetate	α 18·5	204	20	0·8611	1·4408	87·14	30·95	778·7	8·05
	β 22·1	(18 mm.)	25	0·8577	—	—	30·5	778·9	6·75
Ethyl malonate	—	199·3	20	1·0547	1·4139	37·93	31·9	360·8	2·15
			25	1·0494	—	—	31·3	360·8	1·94
Ethyl succinate	—	216·6	20	1·0402	1·4200	42·33	31·9	397·8	2·81
			25	1·0353	—	—	31·3	397·8	2·48
Ethyl adipate	−22	251	20	1·0076	1·4272	51·53	32·5	479·0	3·50
			25	1·0034	—	—	32·0	479·0	3·08
Ethyl suberate	—	283	20	0·9827	1·4325	60·81	32·75	560·3	4·74
			25	0·9783	—	—	32·2	560·5	4·17
Ethyl azelate	−19·8	172	20	0·9732	1·4344	65·40	32·85	600·7	5·32
		(18 mm.)	25	0·9692	—	—	32·35	600·9	4·65
Ethyl sebacate	+1·65	184	20	0·9631	1·4364	70·15	33·0	642·6	5·96
		(18 mm.)	25	0·9591	—	—	32·45	642·5	5·18
Ethyl ethylmalonate	—	208·2	20	1·0082	1·4164	46·86	29·8	436·0	2·41
			25	1·0037	—	—	29·1	435·4	2·15
Ethyl *n*-butylmalonate	—	239·0	20	0·9749	1·4226	56·42	29·1	515·0	3·47
			25	0·9703	—	—	28·55	515·0	3·02
Ethyl *n*-hexadecylmalonate	α 12·7	241	20	0·9118	1·4443	112·04	31·45	998·3	18·2
	β 25·1	(9·5 mm.)	25	0·9080	—	—	30·95	998·4	14·9
Ethyl benzoate	—	212·2	20	1·0468	1·5051	41·56	35·4	349·7	2·22
			25	1·0421	—	—	34·75	349·7	1·99
Ethyl chloroformate	—	92·6	20	1·1392	1·3952	22·84	26·1	215·3	0·557
			25	1·1325	—	—	25·45	215·2	0·528
Methyl chloroacetate	—	129·6	20	1·2345	1·4214	22·31	35·2	214·1	1·143
			25	1·2281	—	—	34·5	214·1	1·048
Ethyl chloroacetate	—	143·1	20	1·1510	1·4212	27·00	32·0	253·2	1·194
			25	1·1446	—	—	31·35	253·3	1·096
n-Propyl chloroacetate	—	162·9	20	1·1038	1·4253	31·65	30·95	291·7	1·50
			25	1·0977	—	—	30·35	291·9	1·365
n-Butyl chloroacetate	—	181·7	20	1·0707	1·4291	36·26	30·4	330·2	1·71
			25	1·0652	—	—	29·8	330·2	1·55

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	t.	d_4^t.	n_D^t.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
Methyl dichloroacetate	—	143·9°	20°	1·3786	1·4424	27·46	34·0	250·4	1·546
			25	1·3712	—	—	33·25	250·4	1·414
Ethyl dichloroacetate	—	157·3	20	1·2804	1·4375	32·15	31·35	290·1	1·60
			25	1·2734	—	—	30·75	290·3	1·46
n-Propyl dichloroacetate		175·7	20	1·2234	1·4402	36·85	30·65	328·9	1·91
			25	1·2171	—	—	30·1	329·1	1·74
n-Butyl dichloroacetate	—	194·8	20	1·1841	1·4420	41·34	30·1	366·0	2·20
			25	1·1783	—	—	29·5	365·9	1·98
Methyl trichloroacetate	—	153·4	20	1·4870	1·4565	32·46	33·0	286·0	1·85
			25	1·4800	—	—	32·3	285·8	1·69
Ethyl trichloroacetate	—	167·3	20	1·3841	1·4501	37·17	30·8	325·8	1·72
			25	1·3773	—	—	30·2	325·8	1·57
n-Propyl trichloroacetate	—	185·5	20	1·3187	1·4507	41·93	30·6	366·4	2·04
			25	1·3123	—	—	30·05	366·5	1·86
n-Butyl trichloroacetate	—	206·0	20	1·2736	1·4514	46·43	30·55	405·1	2·38
			25	1·2674	—	—	30·0	405·2	2·14
2-Chloroethyl acetate	—	145·1	20	1·1556	1·4230	27·02	33·6	255·3	1·61
			25	1·1492	—	—	32·9	255·5	1·46
2-Chloroethyl chloroacetate	—	202·7	20	1·3584	1·4624	31·79	41·5	293·3	4·27
			25	1·3520	—	—	40·8	293·4	3·73
2-Chloroethyl dichloroacetate	—	213·0	20	1·4570	1·4738	36·91	39·8	330·0	5·09
			25	1·4504	—	—	39·1	330·0	4·41
2-Chloroethyl trichloroacetate	—	217·5	20	1·5329	1·4805	41·90	37·3	364·1	5·43
			25	1·5262	—	—	36·6	364·0	4·70
Ethyl β-chloropropionate	—	162·4	20	1·1044	1·4253	31·63	31·65	293·2	1·625
			25	1·0994	—	—	31·1	293·3	1·48
Diethyl sulphide	—	92·1	20	0·8367	1·4425	28·47	25·3	241·6	0·446
			25	0·8316	—	—	24·7	241·6	0·422
Di-*n*-butyl sulphide	—	188·1	20	0·8388	1·4525	47·07	27·35	398·6	1·072
			25	0·8348	—	—	26·8	398·5	0·995
Di*iso*butyl sulphide	—	170·0	20	0·8285	1·4471	47·16	25·1	395·0	0·944
			25	0·8244	—	—	24·6	395·0	0·880
Di*iso*amyl sulphide	—	215·3	20	0·8341	1·4531	56·48	26·3	473·0	1·525
			25	0·8303	—	—	25·85	473·2	1·395
2-Chlorodiethyl sulphide	—	59 (20 mm.)	20	1·0758	1·4898	33·47	33·1	277·8	—
2 : 2′-Dichlorodiethyl sulphide	14·4°	107 (15 mm.)	20	1·2746	1·5270	38·36	42·7	319·0	4·3
2-Chloroethyl 1 : 2-dichlorovinyl sulphide	—	107 (15 mm.)	20	1·4315	1·5562	43·01	40·9	338·3	2·8
2-Chloroethyl 1 : 2 : 2-trichlorovinyl sulphide	—	123 (15 mm.)	20	1·5425	1·5700	48·06	41·7	372·3	3·9
1 : 1 : 2-Trichloroethyl 2-chlorovinyl sulphide	—	122·5 (15 mm.)	20	1·5404	1·5661	47·85	41·7	372·8	5·7
1 : 2 : 2-Trichloroethyl 1 : 2-dichlorovinyl sulphide	—	134·5 (15 mm.)	20	1·6293	1·5778	53·02	41·8	406·2	6·5
1 : 1 : 2 : 2 : 2 : 2′-Hexachlorodiethyl sulphide	—	158·5 (15 mm.)	20	1·6849	1·5683	57·66	43·45	452·6	25·4
1 : 1 : 1′ : 2 : 2′ : 2′-Hexachlorodiethyl sulphide	—	159·5 (15 mm.)	20	1·6841	1·5681	57·68	43·35	452·5	29·4
1 : 1 : 1′ : 2 : 2 : 2′ : 2′-Heptachlorodiethyl sulphide	—	171 (15 mm.)	20	1·7473	1·5741	62·58	43·2	486·1	42·7
n-Butyl cyanide	—	141	20	0·7993	1·3975	25·06	27·6	238·3	0·753
			25	0·7952	—	—	27·1	238·4	0·705
n-Hexadecyl cyanide	31·7	195 (8 mm.)	30	0·8284	1·4431	80·44	31·35	717·8	7·65
			35	0·8254	—	—	30·85	717·5	6·55

RESULTS (*continued*).

Compound.	F. p.	B. p. (760 mm. except where stated).	*t*.	d^t_4.	n^t_D.	$[R]_D$.	Surface tension (dynes/cm.).	Parachor.	Viscosity (centipoises).
n-Amylamine	—	105·3°	20°	0·7561	1·4115	28·65	25·15	258·1	0·720
			25	0·7519	—	—	24·65	258·3	0·658
n-Propyl alcohol	—	97·2	20	0·8053	1·3862	17·53	23·9	165·0	2·29
			25	0·8016	—	—	23·5	165·0	2·015
n-Butyl alcohol	—	117·9	20	0·8102	1·3992	22·13	24·8	204·1	2·98
			25	0·8066	—	—	24·35	204·1	2·60
*iso*Butyl alcohol	—	108·0	20	0·8030	1·3953	22·13	23·0	202·0	3·82
			25	0·7994	—	—	22·55	201·9	3·24
n-Amyl alcohol	—	137·5	20	0·8146	1·4103	26·81	25·6	243·3	3·68
			25	0·8110	—	—	25·15	243·3	3·19
n-Hexyl alcohol	—	156·6	20	0·8198	1·4174	31·35	26·55	282·8	5·32
			25	0·8164	—	—	26·05	282·7	4·52
n-Heptyl alcohol	—	175·9	20	0·8236	1·4238	35·96	27·25	322·2	7·00
			25	0·8202	—	—	26·75	322·0	5·87
n-Octyl alcohol	—	194·6	20	0·8265	1·4287	40·57	27·9	361·7	9·13
			25	0·8232	—	—	27·4	361·9	7·55
n-Butyric acid	—	163·4	20	0·9585	1·3981	22·18	26·8	209·0	1·72
			25	0·9537	—	—	26·2	208·9	1·57
n-Valeric acid	—	185·6	20	0·9386	1·4085	26·86	27·4	248·8	2·25
			25	0·9342	—	—	26·85	248·7	2·03
n-Hexoic acid	—	205·3	20	0·9271	1·4162	31·44	28·05	288·2	3·22
			25	0·9230	—	—	27·55	288·2	2·87
n-Octoic acid	15·9°	237·7	20	0·9110	1·4279	40·70	29·2	367·8	6·09
			25	0·9070	—	—	28·7	367·8	5·29
n-Nonoic acid	12·0	254·0	20	0·9052	1·4322	45·33	29·7	407·9	8·30
			25	0·9013	—	—	29·2	407·9	7·15

DISCUSSION.

The results obtained, given in the accompanying table, agree in general with those of other workers, and in particular with the recent data of Timmermans and his collaborators (*J. Chim. physique*, 1926, **23**, 747; 1928, **25**, 411; 1930, **27**, 401; 1932, **29**, 529; 1934, **31**, 85; 1935, **32**, 501, 589; 1937, **34**, 693; cf. Roland and Lek, *Bull. Soc. chim. Belg.*, 1931, **40**, 177) and of Vogel (*J.*, 1934, 333; 1943, 16, 637; 1946, 133; 1948, 607 *et seq.*, 1804 *et seq.*).

The only marked discrepancies occur with the surface tensions of the C_6—C_8 alcohols, and one or two other liquids of high viscosity, where the capillary rise method used by these workers appears to give low and erratic results. The discontinuity in surface tension at C_7 in the alcohol series noted by Smith and Sorg (*J. Physical Chem.*, 1941, **45**, 671) has not been confirmed.

In view of the incompleteness of the investigation, and of the recent extensive work of Vogel in the same field, little useful purpose would be served by detailed analysis of the results now reported. A few points, however, merit brief discussion.

First, as regards the CH_2 parachor increment: The present measurements of parachor increase from C_4 to C_{16} in nine different aliphatic series support a mean increment of 40 units originally advocated in our earlier paper and now accepted by Vogel on the basis of his own data. It must, however, be appreciated that this is a representative average value, and that owing to slight variation of the exponent in the Kleeman–MacLeod relation, $\gamma = C(D - d)^4$, from compound to compound, the observed increment in any given case depends both on the temperature range of measurement, and on the particular series being examined and the number of terms considered. The parachor is, in fact, not strictly a constant, and only approximately homologously additive.

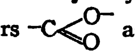
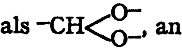
The atomic and group constants previously evaluated on the basis of this increment reproduce satisfactorily the parachor data now reported, and would not therefore appear to require significant modification. Such constants are, not unnaturally, much the same as those recently put forward by Vogel on the same basis, as will be seen from the subjoined tabular summary of the more important values.

Atom or Group.	*P* value. M. & P.	*P* value. V.	Atom or Group.	*P* value. M. & P.	*P* value. V.
CH_2	40	40·0	Cl	55	55·2
H in CH_2	15·4	15·7	Br	69	68·8
C in CH_2	9·2	8·6	I	90	90·3
CH_3	55·4	55·4	CN	64·7	64·6
C_2H_5	95·4	95·4	O in ethers	20	19·8
Allyl	123·6	124·3	S in sulphides	50	48·6
Phenyl	190	188·3	CO_2– in esters	65·2	63·4
Double bond	19	19·9	OH in alcohols	30	30·2
6-Ring	0·8	1·4	CO_2H	75·2	73·7

M. & P. = Mumford and Phillips *J.*, 1929, 2112 (Table I).
V. = Vogel, *J.*, 1948, 1833 (Table XXII).

In the case of many atoms and groups (*e.g.*, halogen, ethereal oxygen, cyanogen, etc.) the two sets of constants are indeed virtually identical, though with certain of the more complex groupings (*e.g.*, phenyl, CO·O in esters) they differ by one or more units. Vogel's values are based on much more extensive data, but any resulting gain in accuracy would appear to be largely offset by the circumstance that each group value has been independently evaluated, and cannot be quantitatively computed by summation of its component atomic and structural constants. This applies, rather illogically, to the lower alkyl groups themselves in Vogel's system, in which the successive CH_2 differences from methyl to octyl are given as 40, 39·9, 39·8, 39·7, 40, 40·7, and 40, respectively, one curious result of this being that the calculated parachor of, say, *n*-hexane, varies according to whether it is considered as *n*-hexyl + H (270·7), *n*-amyl + methyl (270·4), *n*-butyl + ethyl (270·7), di-*n*-propyl (271·0), $4CH_2$ + 2 methyl (270·8), or $6CH_2 + 2H$ (271·4).

The decrement of 3 units previously noted as applying to branched-chain groups of the type $-CHR_2$ receives support from the parachors of the few *iso*-compounds now reported, and it is interesting to note in this connection that according to Vogel the parachor values of *iso*- and *sec.*-alkyl groups range from 1·5 (*iso*butyl) to 4·1 (*sec.*-butyl) units lower than those of the corresponding *n*-groups.

The well-defined parachor defect associated with accumulation of negative atoms and groups (X) around a central carbon atom would appear to depend to a rather greater extent than was originally surmised on the size and polarity of the atoms and groups concerned, but the parachors now reported, and other recently recorded data, confirm in general the earlier conclusion that for X = Cl, OEt, CO_2Et, and for similar groups the decrement (" strain constant ") associated with $-CHX_2$ groups may be taken as 3 units, with $-CX_3$ groups 6 units, and with compounds of the type CX_4 9 units, within the limits of experimental error; and further, that for such atoms and groups the more complex effect of accumulation on adjacent carbon atoms can be adequately estimated in the manner previously outlined. The depressive effect of negative accumulation on the parachor has been recognised by Vogel in his latest paper (*loc. cit.*), but qualitatively only, and apparently without full appreciation of its applicability, for example, to esters  $-C{<}^{O-}_{O}$ as in acetals  $-CH{<}^{O-}_{O-}$, and of its occurrence to a varying extent in the chlorides and oxychlorides of phosphorus and sulphur, and in many of the esters of the inorganic acids (cf. Table VIII in our original paper).

The general validity of parachors calculated in accordance with the scheme outlined in that table has received additional support from the measurements of Pearson and Robinson (*J.*, 1933, 1427) on sulphur hexafluoride, and of Denbigh and Whytlaw-Grey (*J.*, 1934, 1346) on disulphur decafluoride. In both cases, allowing a " strain constant," due to accumulation, of -15 units per S^{vi} atom, and assuming that the valencies of the latter comprise two co-valent bonds and four " singlet " linkages, the values obtained for the latter linkage ($-11·2$ and $-11·1$, respectively) agree closely with similar values derived from other compounds, *e.g.*, tellurium tetrachloride ($-11·4$; Simons, *J. Amer. Chem. Soc.*, 1930, **52**, 3488; with Te = 79) and phosphorus pentachloride ($-10·5$; Sugden, *J.*, 1927, 1173). The " strain constant " would here appear to connote the screening effect of the surrounding halogens on the central atom, and to be distinct from the defect attributed, following Sugden, to " singlet " linkages, which is presumably connected with the formation of bonds involving inner electron orbits.

The need for assuming the presence of such linkages in compounds of this type, and of semi-polar double (" dative ") bonds in the corresponding oxyhalides and esters, can to some extent be avoided by assigning different parachor values to the central atom in its different valency states (cf. previous paper, p. 2125; also Sippel, *Ber.*, 1930, **63**, *B*, 2185; Buehler, *J. Tennessee Acad. Sci.*, 1931, **6**, 27; Hunter and Samuel, *Rec. Trav. chim.*, 1935, **54**, 114). This procedure, however, does not eliminate the depressive effect of accumulation, and moreover leads to inconsistent and improbable atomic values for the elements concerned in their higher valencies. Thus, according to Samuel (*J. Chem. Physics*, 1944, **12**, 167) the atomic parachor of P^{V} is 18·3 in $POCl_3$, though only 11·0 in PCl_5, whilst that for S^{VI}, given as +13·9 in SO_2Cl_2, is, on the same basis (using Sugden's value of 25 for F), −6·7 in SF_6. So far as concerns the "dative" bond, Vogel's conclusion that parachor data provide no evidence for the presence of co-valent double bonds in the esters and oxyhalides of sulphur and phosphorus, as maintained by G. M. Phillips, Hunter, and Sutton (*J.*, 1945, 146), would appear to be well-founded (cf. Wells, *J.*, 1949, 55).

The view previously advanced, that the effective parachor value of the hydrogen atom depends inversely on the electron affinity of the atom to which it is attached, has been discussed in some detail by Pearson and Robinson (*J.*, 1934, 736) and supported and extended by their measurements of the parachors of the non-metallic hydrides (*J.*, 1932, 972; 1934, 730, 880). Confirmation of the lower parachor value of H in OH groups has also been afforded by Vogel for alcohols and acids (*J.*, 1948, 1814), though attributed by him to variation in the parachor of the oxygen atom.

In the light of modern views on structure, a number of the interpretations of deviations from parachor additivity suggested in our previous paper require some modification, and the atomic and structural constants then put forward could doubtless be more precisely evaluated with the aid of the very considerable additional data now available. Taking the system as originally advanced twenty years ago, however, it may be noted that, of the 690 parachor values recorded by Vogel since Part I of his present series (*J.*, 1934, 333), the difference between calculated (Mumford and Phillips) and observed parachors exceeds 2% in only 23 instances (*i.e.*, 3% of the total), whilst for over 80% of the compounds the agreement is within 1%.

Direct comparison with Vogel's system is not possible for the whole of this series, as his method of computation is not at present applicable to many of the complex esters, etc., considered in his earlier papers. Of more than six hundred compounds listed since Part VII of the series (*J.*, 1943, 16), however, only 63 are not computable by the atomic and group constants given by Vogel in his latest paper, these including, *inter alia*, *tert.*-butyl and amyl compounds, naphthalene derivatives, acetylenedicarboxylic esters, aromatic *tert.*-amines, and a variety of polyhalogenated compounds. Exclusion of these, and the few compounds for which surface tension data are not given, leaves 527 compounds of a wide variety of types, whose parachors can be evaluated by both systems; when this is done, the following comparative analysis of results is obtained.

	Percentage of compounds for which the difference between calc. and obs. parachors is		
System of evaluation.	Within 0·5%.	Within 1%.	Above 2%.
Vogel's data (527 compounds).			
Vogel	67·8	88·7	2·1
Mumford and Phillips	52·9	85·5	1·7

It will be seen that the overall agreement is not very different in the two cases, although Vogel's system gives somewhat closer reproducibility with a greater number of compounds. This is not surprising in view of the circumstance that his constants were derived exclusively from the data to which they are now applied. In the following table a similar comparison is made with parachor data from the measurements of Timmermans and his collaborators (*loc. cit.*) and from the determinations reported in this paper, excluding in both instances such multi-branched and polyhalogenated compounds as cannot at present be evaluated by Vogel's system.

	Percentage of compounds for which the difference between calc. and obs. parachors is		
System of evaluation.	Within 0·5%.	Within 1%.	Above 2%.
Timmerman's data (126 compounds).			
Vogel	54·8	79·4	5·5
Mumford and Phillips	54·0	86·5	3·2
Data from present paper (102 compounds).			
Vogel	63·7	89·2	3·0
Mumford and Phillips	63·7	96·0	1·0

The position is here somewhat different, the values calculated according to Vogel showing the smaller overall agreement. It would seem, therefore, that the employment of a multiplicity of independently evaluated and unrelated group constants is a refinement which over-estimates the precision of the parachor, and that there is much to be said for adhering to the scheme advocated in our original paper.

Part of this work was carried out at a Ministry of Supply Establishment, and the authors thank the Chief Scientist of the Ministry for permission to publish the data so obtained.

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20. *The Enzymic Synthesis and Degradation of Starch. Part VI. The Properties of Purified P- and Q-Enzymes.*

By S. A. BARKER, E. J. BOURNE, I. A. WILKINSON, and S. PEAT.

Directions are given for the preparation of the phosphorylase (P-enzyme) and the cross-linking enzyme (Q-enzyme) of potato as stable, freeze-dried powders. The freeze-drying must be carried out in a citrate buffer of pH 6—7, otherwise both enzymes are destroyed.

The purified P-enzyme (fraction P2) contained no maltase and only traces of Q-enzyme or the normal amylases. It showed a slight phosphatase activity on glycerophosphate but not on glucose-1 phosphate.

The purified Q-enzyme (fraction Q3) was substantially free from maltase, the amylases, and phosphatase. It contained a little P-enzyme, equivalent to 5% of that in the original juice.

Fraction P2 has *per se* no effect on the viscosity of starch paste. Q-Enzyme, on the other hand, has a striking liquefying action, in the presence or absence of phosphate.

Q-Enzyme has a strong accelerating effect on the rate of synthesis of polysaccharide from glucose-1 phosphate by P-enzyme. Q-Enzyme is irreversibly inactivated by being precipitated from aqueous solution by acetone.

The conversion of amylose into amylopectin by Q-enzyme is not inhibited by phloridzin. Moreover, the synthetic activity of P-enzyme is only slightly inhibited by phloridzin.

The significance of these observations is discussed in the succeeding paper (Part VII).

THE study of the extraction and the properties of the cross-linking (Q-) enzyme of potato, described in Part IV of this series (Barker, Bourne, and Peat, *J.*, 1949, 1705), has been continued and extended to include, the potato-phosphorylase (P-enzyme) which is separated in the same process. The method of isolation of the two enzymes is diagrammatically represented in Table I.

It was reported in Part IV that precipitates of Q-enzyme could be freeze-dried with little loss of activity if, to the moist precipitate, boiled potato juice were added before it was submitted to freeze-drying. It seemed probable that the boiled juice was simply buffering the enzyme slurry which, in its absence, became acid owing to loss of ammonia from ammonium sulphate. We have now been able to confirm this supposition and to show by the use of suitable buffers that P-enzyme preparations may also be freeze-dried without loss of activity.

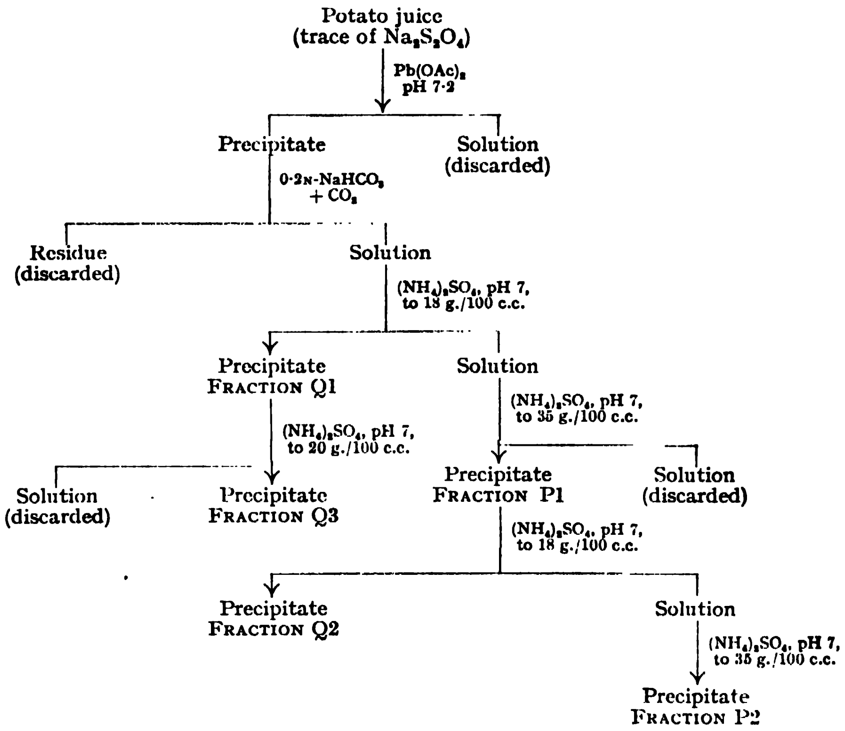
P-Enzyme.—The synthetic activity of fraction P2 (Table I) was completely destroyed by freeze-drying, whereas the less pure fraction, P1, retained about 25% of its activity. During the freeze-drying of the latter fraction the pH fell from 7·3 to *ca.* 5·5 (Table II). Boiled and filtered potato juice stabilised both fractions to freezing and the maximum acidity change was, in this case, from pH 7·2 to 6·4 (Table III). The effect of freeze-drying P1 (and P2) fractions in the presence of different buffers is shown in Tables IV and V. It was concluded that complete retention of the activity of P-enzyme was possible if the freeze-drying was carried out in a 0·2M-citrate buffer of pH 6·0.

Q-Enzyme.—It is shown in Table VI that the activity of Q-enzyme (in the conversion of amylose into amylopectin) is completely retained if a Q3 fraction (see Table I) is freeze-dried in a 0·2M-citrate buffer of pH 6·0, 6·5, or 7·0, and for routine preparations we have adopted the procedure of freeze-drying in such a citrate buffer at pH 7·0. It is a matter of considerable interest that, although a citrate buffer of pH 7·0 allows of maximum retention of Q-activity, yet an acetate buffer of the same pH is quite ineffective. In fact, a Q3 preparation freeze-dried in an acetate buffer of pH 7·0 was almost completely inactivated (Table VI). This loss of activity appears to be associated with the development of acidity during the drying process. The final pH with acetate was 5·15, as compared with 6·5 when citrate was used. Table IV indicates that P-enzyme also is destroyed by freeze-drying in an acetate buffer of pH 7·0.

Stocks of fractions P2 and Q3 were prepared from more than 60 kg. of potatoes during the "resting" stage, *i.e.*, when the amylase content was a minimum, and were freeze-dried in citrate buffers of pH 6·0 and 7·0, respectively. The dry powders were stable during prolonged periods; for instance, the dried fraction P2 lost not more than 1% of its activity in 60 days,

TABLE I.

Isolation of P- and Q-enzymes from potato juice.



whereas the activity of the same sample kept in solution in citrate buffer (pH 6·0) for the same time fell to one-tenth of its initial value. The Q3 powder showed no change in Q-enzyme activity in 41 days.

The Enzymic Purity of Fractions P2 and Q3.—The Q3 fraction was shown in Part IV to be substantially free from the normal amylases and from maltase. It contained a little P-enzyme (detected by its synthetic activity) corresponding, after freeze-drying, to about 5% of the P-enzyme initially present in the juice. The P2 fraction was also shown to be free from maltase (lack of maltose-hydrolysing activity). It contained, at most, only traces of Q-enzyme and the normal amylases inasmuch as it effected, at pH 6—7, only a very slow fall in the A.V. (6800 A.) of amylose.

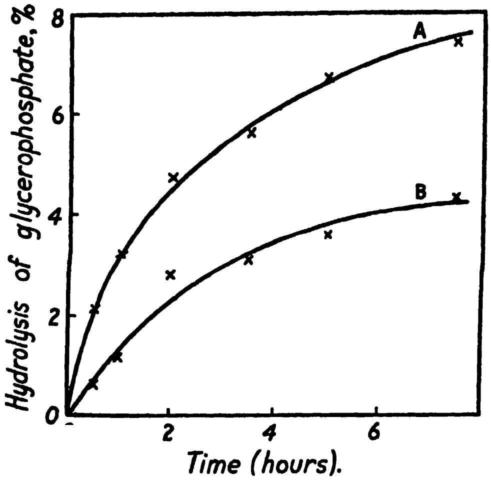
Phosphatase Content.—The Q3 fraction did not liberate a detectable amount of free phosphate from sodium glycerophosphate in 7·5 hours at pH 6·5 and might thus be considered as free from phosphatase. The freeze-dried P2 fraction did, however, contain a trace of phosphatase since it effected a 7·5% conversion of glycerophosphate into free phosphate in 7·5 hours (see Fig. 1, curve *A*). It appeared that this reaction was either reversible or was inhibited by phosphate ion since the hydrolysis of glycerophosphate proceeded much more slowly in the presence of added mineral phosphate (Fig. 1, curve B). Fraction P2 exerted no phosphatase activity with respect to glucose-1 phosphate under the normal conditions of polysaccharide synthesis. Thus, when fraction P2 was incubated at pH 6·0 in the presence of starch with glucose-1 phosphate no development of reducing power occurred in one hour.

Starch-liquefying Action of P- and Q-Enzymes.—The relative viscosity of a 1% dispersion of potato starch in acetate buffer (pH 7·0) was not affected by fraction P2. In a phosphate buffer of pH 6·7, a slow fall in the viscosity was observed (Fig. 2) and could be attributed to normal phosphorolysis of the starch.

It was reported in Part I (Bourne and Peat, *J.*, 1945, 877) that the crude preparations of the branching enzyme then available liquefied starch pastes. That this is an intrinsic action of Q-enzyme has now been demonstrated by the striking diminution of viscosity of a 1% starch paste brought about by the highly purified Q3 fraction (Fig. 2). As pointed out above,

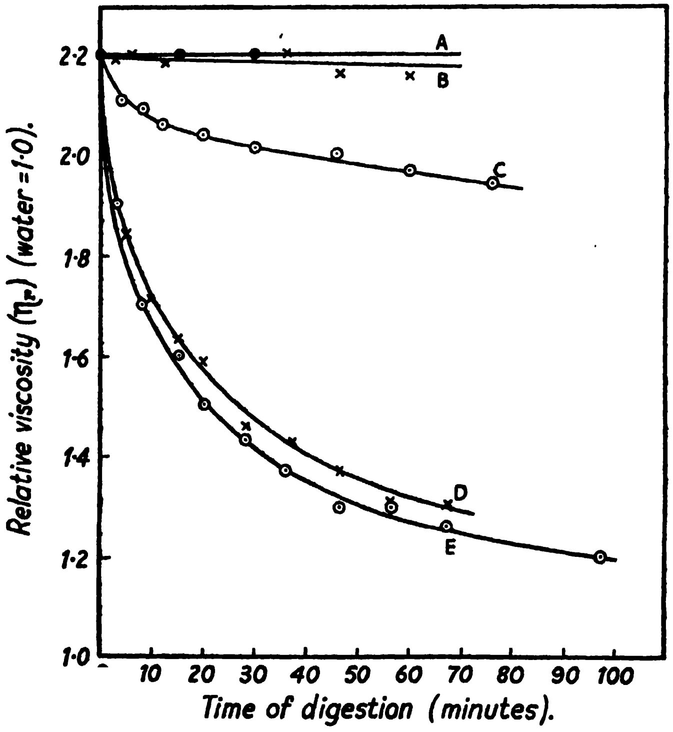
Fig. 1.

Phosphatase activity of enzyme fraction P2 (*sodium glycerophosphate substrate*).



A. Mineral phosphate not added to digest.
B. Mineral phosphate added to digest.

The action of fractions P2 *and* Q3 *on the viscosity of starch paste in the presence and absence of mineral phosphate.*



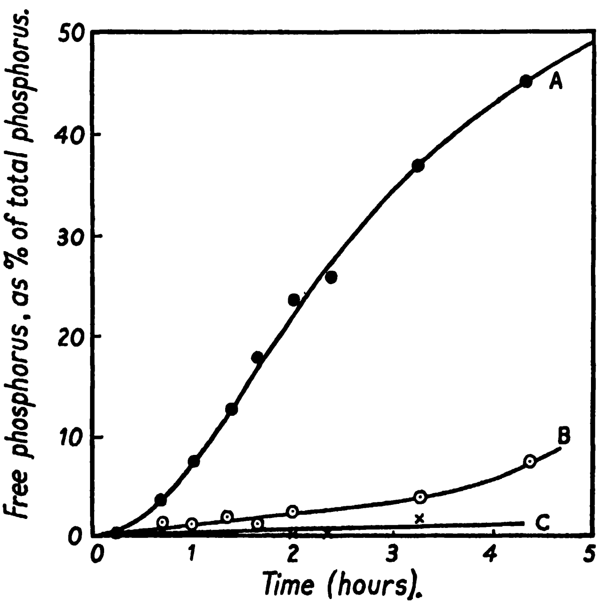
A. Water (acetate buffer). *B.* P$_2$ (*Acetate buffer*).
C. P$_2$ (*Phosphate buffer*). *D.* Q$_3$ (*Acetate buffer*).
E. Q$_3$ (*Phosphate buffer*).

there are reasons for believing that fraction Q3 does not contain α-amylase in sufficient concentration to cause this degree of liquefaction. Nor can the liquefaction be ascribed to phosphorolysis. It is true that a somewhat greater fall in viscosity is registered if mineral phosphate is present in the Q3 digest (Fig. 2), but we ascribe this enhanced effect in the presence of phosphate to the small proportion of P-enzyme which the Q3 fraction contains.

*Autocatalysis in Polysaccharide Syntheses from Glucose-*1 *Phosphate.*—The rate of liberation of free phosphate by P-enzyme acting on glucose-1 phosphate is a measure of the rate of synthesis of polysaccharide, and Fig. 3 shows that this rate is greatly accelerated if Q-enzyme is also present. The enzyme preparations used in this experiment were purified beyond the stages given in Table I, by two further precipitations with ammonium sulphate, giving fractions P4 and Q5. Curve *C* in Fig. 3 shows that the P-enzyme content of fraction Q5 is negligibly small. The autocatalytic effect is shown by the difference between curve *B* (P4 fraction alone) and curve *A* (P4 and Q5 acting together). Cori and Cori (*J. Biol. Chem.*, **1943**, **151**, 57) showed that the " branching factor " of liver and heart had a similar catalytic effect on the synthetic action of muscle phosphorylase, and ascribed the effect to the increase in the proportion of non-reducing chain ends brought about by the branching factor. Clearly Q-enzyme functions in the same way. It has been indicated by Bernfeld and Meutémédian (*Helv. Chim. Acta*, 1948, **31**, 1724) that α-amylase, which fragments amylose chains, would, by increasing the number of chain ends, also catalyse the synthesis from glucose-1 phosphate (see also Part III, Bourne, Peat, and Sitch, this vol., p. 1448). This autocatalytic action cannot therefore be regarded as a specific test for Q-enzyme.

FIG. 3.

*Autocatalysis in polysaccharide synthesis from glucose-*1 *phosphate.*



A. *P-Enzyme + Q-enzyme.*
B. *P-Enzyme alone.*
C. *Q-Enzyme alone.*

The Inactivation of Q-Enzyme by Acetone.—It was shown in Part II (Bourne, Macey, and Peat, *J.*, **1945**, 882) that Q-enzyme was inactivated by precipitation from aqueous solution with ethyl alcohol (3 vols.) whereas salivary α-amylase was unaffected by alcohol. We have now found that the activity of the purified Q-enzyme (fraction Q3) is almost completely destroyed when it is precipitated from a citrate buffer solution at pH 6 and 0° with acetone at concentrations between 25 and 40%.

The Effect of Phloridzin on P- and Q-Enzymes.—Green and Stumpf (*J. Biol. Chem.*, **1942** **142**, 355) reported that potato phosphorylase was partly inhibited (in its synthetic action) by phloridzin. At a phloridzin concentration of (approx.) 1·4 × 10^{-3}M., the inhibition was only

18%, and at half this concentration there was no inhibition of phosphorylase. Bernfeld and Meutémédian (*loc. cit.*, p. 1735) showed that isophosphorylase was not inhibited by phloridzin and, on the assumption that phosphorylase was strongly inhibited by phloridzin, added the latter reagent to mixtures of phosphorylase and isophosphorylase in order to influence the relative active concentrations of the two enzymes.

We have now examined the effect of phloridzin on the conversion of amylose into amylopectin by Q-enzyme and on the synthesis of amylose from glucose-1 phosphate by P-enzyme. Caution had to be observed when measuring the activity of fraction Q3 by diminution of A.V. (6800 A.) for it was shown that phloridzin reacts rapidly with free iodine and also, but more slowly, changes the blue colour of an amylose–iodine complex. To overcome this difficulty when Q-enzyme was incubated with amylose in the presence of phloridzin, more than the standard concentration of iodine was employed and the absorption value was measured immediately after staining. By adopting this technique we were able to show that Q3 fraction was not inhibited at all by $1{\cdot}5 \times 10^{-3}$M-phloridzin (see Table VII).

Furthermore, we found that the introduction of phloridzin ($1{\cdot}24 \times 10^{-3}$M.) into a digest of glucose-1 phosphate and P-enzyme (fraction P2) diminished the enzyme activity by only 8% (Table VIII).

EXPERIMENTAL.

Analytical Methods.—The analytical methods employed were described in Part IV (Barker, Bourne, and Peat, *J.*, 1949, 1705).

Fractionation of Starch.—The amylose samples were isolated from potato starch by precipitation with thymol (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687).

Isolation of P- and Q-Enzymes from Potatoes.—The juice (100 c.c.) from King Edward potatoes was treated with lead acetate and centrifuged. The lead–protein complex was eluted by stirring with sodium hydrogen carbonate in the presence of a stream of carbon dioxide (details of these early stages of the isolation were given in Part IV). To the eluate (*ca.* 110 c.c.) ammonium sulphate solution (pH 7; 50 g./100 c.c.) was added until the concentration of this salt reached 18 g./100 c.c. The precipitate (fraction Q1) was separated by the centrifuge. The concentration of ammonium sulphate in the supernatant liquid was increased to 35 g./100 c.c. and the precipitate (fraction P1) was collected.

Fractionation of P1. Fraction P1 was dissolved in water (20 c.c.) and ammonium sulphate solution (pH 7·0; 50 g./100 c.c.) was added until the salt concentration was 18 g./100 c.c. The precipitate (fraction Q2) was removed and the concentration of ammonium sulphate in the supernatant liquid was increased to 35 g./100 c.c. The precipitate (fraction P2) was collected by the centrifuge.

Fractionation of Q1. Fraction Q1 was dissolved in water (20 c.c.) and kept at 0° for 1 hour. A small insoluble residue was removed before the concentration of ammonium sulphate in the solution was adjusted, as above, to 20 g./100 c.c. The precipitated fraction (Q3) was separated by the centrifuge.

Except where otherwise stated, the operations were carried out at room temperature.

Freeze-drying of P-Enzyme Solutions.—The enzyme solutions were frozen in an alcohol–carbon dioxide mixture and dried at 0·01 mm. No thawing occurred under these conditions. The activities of the enzyme samples were measured by the method of Green and Stumpf (*loc. cit.*).

(a) *Freeze-drying of fractions P1 and P2.* The enzyme fraction (P1 and P2) isolated from 100 c.c. of juice was dissolved in water, and the volume adjusted to 20 c.c. Half of the solution was freeze-dried, the powdery product being redissolved in water and diluted to 10 c.c. The other half served as a control. The results obtained with several different samples of P1 and P2 are given in Table II.

TABLE II.

Freeze-drying of fractions P1 and P2.

Enzyme fraction.	pH of enzyme solution:		Retention of P-enzyme activity during freeze-drying (%).	Enzyme fraction.	pH of enzyme solution:		Retention of P-enzyme activity during freeze-drying (%).
	before drying.	after drying.			before drying.	after drying.	
P1	7·20	5·65	45·7	P1	7·35	5·06	8·6
,,	7·34	5·65	15·8	,,	7·29	5·60	17·7
,,	7·36	5·51	42·6	P2	—	—	0·0
,,	7·24	5·71	35·0	,,	—	—	0·0

(b) *Freeze-drying of fractions P1 and P2 in the presence of boiled potato juice.* A sample of potato juice was boiled for 20 minutes, filtered, and diluted to its original volume with distilled water. To a solution (20 c.c.) of fraction P1 or P2, obtained from 100 c.c. of juice, 5 c.c. of the boiled juice were added and the enzyme solution thus obtained was divided into two equal portions. One of these was freeze-dried, the dry residue being redissolved in water and diluted to 12·5 c.c. The second half served as a control. It was essential that this control should contain boiled juice because, under these conditions, the addition of boiled juice to fraction P1 or P2 increased the activity of the phosphorylase solution by about 15%. The stabilising effect of boiled juice during the freeze-drying of P-enzyme solutions is shown in Table III.

(c) *Freeze-drying of fraction P1 in the presence of different buffers.* The boiled juice used in (b) was replaced by different buffer solutions as shown in the Table IV. It was observed that the mere addition of 0·2M-sodium hydrogen carbonate, even without freeze-drying, diminished the P-enzyme activity by about 30%.

TABLE III.

Freeze-drying of fractions P1 and P2 in the presence of boiled potato juice.

Enzyme fraction.	pH of enzyme solution, containing boiled juice: before drying.	after drying.	Retention of P-enzyme activity during freeze-drying (%).
P1	7·09	6·40	95·0
,,	7·26	6·40	100·0
P2	—	—	100·0

TABLE IV.

Freeze-drying of fraction P1 in the presence of different buffers.

Buffer solution.	Volume of buffer added to 20 c.c. of P1 solution (c.c.).	Retention of P-enzyme activity during freeze-drying (%).
0·1M-Citrate (pH 6·3)	4·0	66·8
0·1M-Glycine (pH 8·2)	,,	59·5
1·0M-Acetate (pH 7·0)	,,	0·0
0·2M-$NaHCO_3$	,,	47·2
,,	,,	53·0
,,	,,	51·8
0·5M-$NaHCO_3$	8·0	29·4
,,	,,	51·5

(d) *Freeze-drying of solutions of fractions P1 and P2 in* 0·2M-*citrate buffer* (*pH* 6·0). Fraction P1 (or P2), isolated from 100 c.c. of potato juice, was dissolved directly in 0·2M-citrate buffer (pH 6·0) to give 20 c.c. of enzyme solution, half of which served as a control. The other half was freeze-dried, the product being redissolved in water and diluted to 10 c.c. The efficacy of the citrate buffer as a stabiliser during the freeze-drying of P1 and P2 fractions is shown in Table V, where the results obtained with several different samples of these enzymes are recorded.

TABLE V.

Freeze-drying of solutions of fractions P1 and P2 in 0·2M-*citrate buffer* (*pH* 6·0).

Enzyme fraction	P1	P1	P1	P1	P2	P2
Retention of P-enzyme activity during freeze-drying (%)	100·0	98·5	100·0	100·0	100·0	100·0

In view of the above results, this method of freeze-drying fractions P1 and P2 in 0·2M-citrate buffer (pH 6·0; 20 c.c. for each 100 c.c. of juice originally used) was adopted as the standard method for the preparation of the enzymes in powder form, and has been successfully employed for the isolation and storage of the P-enzyme from more than 60 kg. of potatoes.

Freeze-drying of Fraction Q3 in the Presence of Citrate and Acetate Buffers.—Fraction Q3, isolated from 125 c.c. of juice, was dissolved in 0·2M-citrate buffer (pH 6·0; 25 c.c.). A portion (20 c.c.) of this solution was freeze-dried, as above, the rest being retained as a control. The dry powder was dissolved in water, diluted to 20 c.c., and incorporated in a digest consisting of amylose solution (14 mg. in 7·5 c.c., prepared as in Part IV), maltose solution (3·0 mg. in 1·5 c.c.), 0·2M-citrate buffer (pH 6·0; 3 c.c.), and the buffered enzyme solution (2·0 c.c.), making a total volume of 14·0 c.c. A second digest contained the enzyme control. After 30 minutes at 20·5° an aliquot portion (1·0 c.c.) of each digest was stained with iodine (2·0 mg.)–potassium iodide (20·0 mg.) in a final volume of 100 c.c. and the A.V. (6800 A.) was measured in the usual manner.

In three similar experiments the 0·2M-citrate buffer (pH 6·0) was replaced, both during freeze-drying and in the digests, by other buffers, namely, 0·2M-citrate buffer (pH 6·5), 0·2M-citrate buffer (pH 7·0), and 0·2M-acetate buffer (pH 7·0). The results are shown in Table VI.

TABLE VI.

Freeze-drying of solutions of fraction Q3 in acetate and citrate buffers.

Buffer used during freeze-drying and in the digests.	Fall (%) in A.V. (6800 A.) in 30 mins. Control.	After freeze-drying.	pH of enzyme-buffer solution after freeze-drying.
0·2M-Citrate (pH 6·0)	74·7	72·6	5·83
0·2M-Citrate (pH 6·5)	79·4	76·8	6·21
0·2M-Citrate (pH 7·0)	79·5	76·8	6·51
0·2M-Acetate (pH 7·0)	74·5	0·8	5·15

For routine purposes, the standard technique adopted for the freeze-drying of fraction Q3 was to dissolve the enzyme in 0·2M-citrate buffer (pH 7·0; 12·5 c.c. for each 100 c.c. of juice), freeze the solution in an alcohol–carbon dioxide mixture, and dry it at 0·01 mm. In this way a very active enzyme preparation has been obtained in powder form from more than 60 kg. of potatoes.

The Stability of Fractions P1 and P2 when stored at 0°.—Fraction P1 was dissolved in 0·2M-citrate buffer (pH 6·0; 20 c.c. for each 100 c.c. of juice originally employed) and the solution was divided into two parts. One of these was freeze-dried as above, the other being kept as a control. The solution and the dry powder were stored at 0° in tightly-stoppered bottles, and the P-enzyme activity of each was measured at intervals by the method of Green and Stumpf (*loc. cit.*). In a second experiment fraction P2 was used. The rates of decay in P-enzyme activity are shown below.

The stabilities of fractions P1 and P2 in citrate buffer (pH 6·0) at 0°.

Enzyme fraction.	Method of storage.	Retention of P-enzyme activity (%). 12 days.	27 days.	60 days.
P1	Solution	94·2	83·5	60·0
,,	Powder	100·0	99·0	98·0
P2	Solution	59·0	49·5	9·1
,,	Powder	100·0	100·0	99·0

The Stability of Fraction Q3 when stored at 0° as a Powder.—Fraction Q3 was dissolved in 0·2M-citrate buffer (pH 7·0) and freeze-dried according to the standard technique described above. The powder was stored at 0° in a well-stoppered bottle, samples being periodically removed and incubated with amylose in the manner already described. The figures quoted in the following table show that there was no detectable loss in Q-enzyme activity in 41 days.

The stability of fraction Q3 when stored at 0° in powder form.

Time of storage (days)	10	27	41
Fall (%) in A.V. (6800 A.) of amylose in 30 mins.	75·0	75·2	75·1

Tests for Phosphatase in Fractions P2 and Q3.—The enzyme fractions (P2 and Q3) used in these tests had been stored for several weeks as the dry powders obtained when their solutions in 0·2M-citrate buffers were freeze-dried under the standard conditions already described.

(a) *With sodium glycerophosphate as substrate for fraction P2.* The solutions used were 0·1M-sodium glycerophosphate in 0·2M-citrate buffer (pH 6·5), potassium dihydrogen phosphate in water (*ca.* 3·2 mg. phosphorus/c.c.), and fraction P2 in water (40 c.c. for each 100 c.c. of juice employed for the isolation of the enzyme). These solutions were incorporated in four digests (A—D), the compositions of which are shown in section (i) of the following table. The digests were incubated at 20° and free-phosphate estimations were made periodically; these are recorded in section (ii).

Action of fraction P2 on sodium glycerophosphate.

(i) *Compositions of digests.*

Solution.	Digest, c.c. A.	B.	C.	D.
Sodium glycerophosphate	10	10	10	10
Fraction P2	4	4	—	—
Potassium dihydrogen phosphate	1	—	1	—
Water	—	1	4	5

(ii) *Free phosphate estimations.*

Time of incubation (hours).	Free phosphorus (mg. per 15 c.c. digest). A.	B.	C.	D.
0·5	3·420	0·673	3·210	0·000
1·0	3·570	1·020	—	—
2·0	4·080	1·485	—	—
3·5	4·170	1·760	—	—
5·0	4·350	2·100	—	—
7·5	4·560	2·310	3·210	—

The inorganic phosphate liberated by enzyme action was measured (i) in the presence of potassium dihydrogen phosphate by the difference between digest (A) and (C), and (ii) in the absence of potassium dihydrogen phosphate by the difference between digest (B) and (D). These values are plotted in Fig. 1.

(b) *With sodium glycerophosphate as substrate for fraction Q3.* The above experiment was repeated using a solution of fraction Q3 in water (40 c.c. for each 100 c.c. of juice employed for the isolation of the enzyme) instead of the solution of fraction P2. No mineral phosphate was liberated by enzyme action in digest (B) in 7·5 hours, showing the absence of phosphatase activity in fraction Q3.

(c) *With dipotassium glucose-1 phosphate as substrate for fraction P2.* A digest containing the solution of fraction P2 (1·5 c.c.) used in (a), 0·1M-dipotassium glucose-1 phosphate in 0·2M-citrate buffer (pH 6·0; 1·0 c.c.), 0·5M-citrate buffer (pH 6·0; 0·5 c.c.), and starch solution (0·5 c.c., containing 0·5 mg. of starch) was incubated at 20·5° for 1 hour. There was no increase in reducing power, thus proving the absence, under these conditions, of phosphatase action on the glucose-1 phosphate.

The Influence of Fractions P2 and Q3 on the Viscosities of Starch Pastes in the Absence and in the Presence of Mineral Phosphate.—*Enzyme solutions.* The P2 and Q3 enzyme fractions, which had been stored at 0° for several weeks after being freeze-dried by the standard methods given above, were each dissolved in water (20 c.c. for each 100 c.c. of juice used for the isolation of the enzymes). The P2 solution contained 14·1 units of phosphorylase/c.c., and the Q3 solution 0·8 unit of phosphorylase/c.c. In a preliminary experiment it was shown that this Q3 solution effected a maximum diminution of 83% in the A.V. (6800 A.) of amylose (B.V., 1·04) with only 2·4% "apparent conversion into maltose," a fact which established the absence of more than traces of the normal amylases from the enzyme sample (see Barker, Bourne, and Peat, Part IV, *loc. cit.*).

Starch pastes. Potato starch (dry weight, 5 g.) was dispersed in boiling water containing sodium chloride (0·5 g.). The solution was cooled and diluted to 450 c.c. with water. To half of this solution 0·2M-acetate buffer (pH 7·0; 25 c.c.) was added, giving solution (A). To the other half 0·2M-phosphate buffer (pH 6·7; 25 c.c.) was added, giving solution (B). The concentrations of starch and buffer in both (A) and (B) were 1% and 0·02M., respectively.

Viscosity measurements. The starch solution (10 c.c.; A or B) and enzyme solution (1 c.c.; P2 or Q3) were adjusted to 20°, mixed, and introduced into an Ostwald viscometer, which was immersed in a thermostat at 20°. Viscosity measurements were made at intervals and are plotted in Fig. 2. In a second series of experiments, in which the volumes of the two buffers employed were increased from 25 c.c. to 75 c.c., similar results were obtained.

The Effect of Phloridzin on the Amylose–Iodine Stain.—Amylose was stained with iodine under the standard conditions for the estimation of B.V. (Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924). The coloured solution contained amylose (1 mg./100 c.c.), iodine (2 mg./100 c.c.), and potassium iodide (20 mg./100 c.c.). A second portion of amylose was stained in the same way except that the final coloured solution contained, in addition, phloridzin (to $3{\cdot}33 \times 10^{-5}$M.). The absorption values, measured immediately after the preparation of the solutions, are shown below. The amylose–iodine stain slowly faded in the presence of phloridzin, indicating that the initial rapid reaction of this compound with the excess of iodine (revealed in the relative absorption values) was followed by a slower reaction with the iodine involved in complex formation with the amylose.

The effect of phloridzin on the amylose–iodine stain.

Phloridzin concentration.	Absorption value at λ (in A.) :							
	4300.	4700.	4900.	5200.	5500.	5800.	6000.	6800.
$3{\cdot}33 \times 10^{-5}$M.	0·40	0·42	0·44	0·51	0·71	0·94	1·04	1·08
Nil	0·63	0·54	0·54	0·59	0·75	0·97	1·07	1·11

The Effect of Phloridzin on the Conversion of Amylose by Fraction Q3.—Enzyme fraction Q3 was incubated with amylose (B.V., 1·30) under the conditions of the standard digest described by Barker, Bourne, and Peat (Part IV, *loc. cit.*). A second digest included the same components together with phloridzin ($1{\cdot}5 \times 10^{-3}$M.). The course of each reaction was followed by staining, at intervals, an aliquot portion (1 c.c. ≡ 1 mg. of amylose) of the digest with iodine (6 mg.) and potassium iodide (60 mg.) in a total volume of 100 c.c. The absorption values of the stained solutions, which were measured as soon as possible after staining, are recorded in Table VII, from which it is seen that phloridzin does not inhibit the action of Q-enzyme on amylose under the conditions of the experiment.

TABLE VII.

The effect of phloridzin on the conversion of amylose (B.V., 1·30) by fraction Q3.

Concentration of phloridzin in digest.	A.V. (6800 A.) after :		
	15 mins.	30 mins.	63 mins.
0	0·602	0·473	0·368
$1{\cdot}5 \times 10^{-3}$M.	0·602	0·467	0·352

Inhibition of P-Enzyme by Phloridzin.—(a) *Inhibition in the digest.* Fraction P2, which had been stored at 0° as the powder obtained when a solution in citrate buffer was freeze-dried by the standard technique described above, was dissolved in water (13·5 c.c. for each 100 c.c. of juice used in the preparation of the enzyme). This solution was incorporated in a digest which contained P2 solution (0·5 c.c.), 1% soluble starch solution (0·5 c.c.), 0·1M-glucose-1 phosphate in 0·2M-citrate buffer (pH 6·0; 1·0 c.c.), and water (1·5 c.c.). The digest was incubated at 35° for 12 minutes, and the reaction was then arrested by addition of 5% trichloroacetic acid solution (5·0 c.c.). After centrifuging, the free phosphate in the supernatant liquid was determined colorimetrically. The free phosphate originally present in the digest was determined by adding the trichloroacetic acid to the digest before the P2 solution was added. The mineral phosphate liberated by enzyme action was calculated by difference.

In other digests, the water (1·5 c.c.) was replaced by phloridzin solutions (1·5 c.c.) of different concentrations (0 to $2{\cdot}9 \times 10^{-3}$M.), and, by comparison with the above control, the effect of phloridzin on P-enzyme activity was determined; the results are given in Table VIII. Phloridzin does not interfere with the estimation of free phosphate.

TABLE VIII.

Inhibition of P-enzyme by phloridzin present in the digest.

Concentration of phloridzin in digest (M. × 10^{-3}) ...	0·00	0·44	0·89	1·06	1·24
Inhibition (%) of P-enzyme activity	0·0	2·2	6·6	8·1	8·1

When the solution of fraction P2 was diluted ten-fold and the concentration of phloridzin in the digest was increased to 2·67 × 10^{-3}M., there was 40·5% inhibition of P-enzyme activity.

(b) *Pretreatment of fraction P2 with phloridzin.* The experiment (a) was repeated with one variation. Fraction P2 was dissolved directly in phloridzin solutions of different concentrations (40 c.c. for each 100 c.c. of juice used in the preparation of the enzyme) and kept at room temperature for 1 hour. A portion (1·5 c.c.) of each solution was added, together with water (0·5 c.c.), to the other components of the digest and the experiment was continued as above, giving the results recorded below.

Inhibition of P-enzyme by pretreatment with phloridzin.

Concentration of phloridzin (M. × 10^{-3}).		Inhibition (%) of P-enzyme activity.
During pretreatment of the enzyme.	In the digest.	
0·00	0·00	0·0
2·07	0·89	7·4
3·10	1·33	10·3
4·14	1·78	14·0
6·20	2·67	21·3

Precipitation of Fraction Q3 with Acetone.—The following operations were performed at 0° in a cold room. Fraction Q3, which had been freeze-dried in citrate buffer in the usual way and stored at 0° for 7 weeks, was dissolved in water (40 c.c. for each 100 c.c. of juice used in the isolation of the enzyme). Portions (2·0 c.c.) of this solution were mixed with aqueous acetone solutions (4·0 c.c.) containing different concentrations of acetone. Each precipitate was collected by the centrifuge and stirred with a mixture of 0·2M-citrate buffer (pH 7·0; 2·0 c.c.) and 0·2M-sodium hydrogen carbonate solution (1·0 c.c.), the insoluble residue being removed by the centrifuge. An aliquot portion (2·0 c.c.) of each supernatant liquid was incubated at 20·5° with amylose (14 mg.; B.V., 1·04), maltose (3 mg.), and 0·2M-citrate buffer (pH 7·0; 2·5 c.c.) in a total volume of 14 c.c. As a control a portion (2·0 c.c.) of the original Q3 solution was mixed with 0·2M-sodium hydrogen carbonate solution (1·0 c.c.) and an aliquot portion (2·0 c.c.) of the mixture was incubated with amylose under the same conditions. After 30 minutes a sample (1·0 c.c.) of each digest was stained with iodine (2 mg.)–potassium iodide (20 mg.) in a total volume of 100 c.c. The values for A.V. (6800 A.) thus obtained are tabulated below.

The precipitation of fraction Q3 with acetone at 0°.

Conc. of acetone (% by vol.)	Control	26·6	33·0	40·0
Fall (%) in A.V. (6800 A.) of amylose in 30 mins.	72·5	8·5	6·7	4·1

Autocatalysis in Polysaccharide Synthesis by P- and Q-Enzymes.—Fraction P2 was further purified by two precipitations with neutral ammonium sulphate, the fraction precipitated between ammonium sulphate concentrations of 19 and 34 g./100 c.c. being collected each time. The product was dissolved in 0·2M-citrate buffer (pH 6·0; 20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzyme) and freeze-dried. When required, the powder was dissolved in water (50 c.c. for each 100 c.c. of juice employed), giving a solution of P-enzyme which contained 2·5 units (Green and Stumpf) of phosphorylase per c.c.

Fraction Q3 was further purified by precipitating it twice with ammonium sulphate (18 g./100 c.c.) in the usual manner. The product was dissolved in 0·2M-citrate buffer (pH 6·5; 13 c.c. for each 100 c.c. of juice used for the isolation of the enzyme) and freeze-dried. When required, the powder was dissolved in water (20 c.c. for each 100 c.c. of juice employed), giving a solution of Q-enzyme which possessed 65% of the Q-enzyme activity present in the original Q3 fraction (measured by incubation with amylose and comparison with dilution curves for Q3). The solution of the purified Q-enzyme contained only 0·05 unit (Green and Stumpf) of phosphorylase per c.c.

These solutions of the purified enzymes were incorporated in digests which contained P-enzyme solution (6·75 c.c.) and/or Q-enzyme solution (6·75 c.c.), together with 0·1M-dipotassium glucose-1 phosphate (9·0 c.c.) and sufficient 0·2M-citrate buffer (pH 6·5) to make the total volume 31·5 c.c. The digests were incubated at 20° and free phosphate estimations were made at intervals, as shown in Fig. 3.

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THE UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

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21. *The Enzymic Synthesis and Degradation of Starch. Part VII. The Mechanism of Q-Enzyme Action.*

By S. A. Barker, E. J. Bourne, I. A. Wilkinson, and S. Peat.

The results reported in the earlier communications in this series are reviewed and correlated with the observations recorded in this paper. Evidence is given which proves, beyond reasonable doubt, that Q-enzyme functions by a non-phosphorolytic mechanism. In this and in other properties it appears to be distinct from the *iso*phosphorylase isolated (also from potatoes) by Bernfeld and Meutémédian (*loc. cit.*).

It is concluded that Q-enzyme is a transglucosidase, but not of the phosphorylase type, and that two amylopectin-synthesising systems represented by Q-enzyme and *iso*phosphorylase may exist together in the potato.

Our work on the enzymic synthesis and degradation of starch has now reached a stage where it is desirable to review the results reported in a series of earlier communications (Part I, Bourne and Peat, *J.*, 1945, 877; Part II, Bourne, Macey, and Peat, *J.*, 1945, 882; Part III, Bourne, Sitch and Peat, *J.*, 1949, 1448; Parts IV and V, Barker, Bourne, and Peat, *J.*, 1949, 1705, 1712; Part VI, Barker, Bourne, Wilkinson, and Peat, preceding paper) and to correlate them with the observations recorded in this paper.

In 1944 Haworth, Peat, and Bourne (*Nature*, **154**, 236) reported the isolation from potatoes of an enzyme (Q-enzyme) which catalysed, in association with potato phosphorylase (P-enzyme), the synthesis of amylopectin from glucose-1 phosphate. We were unaware at that time of the " branching factor " prepared from heart, liver, and yeast by Cori *et al.* (*J. Biol. Chem.*, 1943, **151**, 57) which played a similar rôle in the synthesis of glycogen. Shortly afterwards we advanced a hypothesis to account for the properties of Q-enzyme, from which it was inferred that natural amylose could be converted into amylopectin by the agency of this enzyme (Parts I and II). This hypothesis was subsequently substantiated and a preliminary account was given by Peat, Bourne, and Barker (*Nature*, 1948, **161**, 127) of the conversion of amylose into amylopectin. In no case during the isolation and purification of Q-enzyme or during the investigation of its functions was mineral phosphate introduced and for this reason we have always held the view that Q-enzyme operated by a non-phosphorolytic mechanism.

Recently, Bernfeld and Meutémédian (*Helv. Chim. Acta*, 1948, **31**, 1724, 1735) described the isolation from potatoes of an enzyme (named by them, *iso*phosphorylase) which bore some resemblance to Q-enzyme inasmuch as it played a part in the formation of amylopectin from both amylose and glucose-1 phosphate. There was nevertheless a fundamental difference between the two. Whereas we postulated that phosphate-transfer was not involved in the formation of cross linkages by Q-enzyme, the Swiss authors claimed that such transfers were an integral part of the cross-linking mechanism.

Since *iso*phosphorylase induces no qualitative change in the characteristic blue-staining property of amylose unless mineral phosphate and phosphorylase are present, Bernfeld and Meutémédian suggest that the new enzyme functions by catalysing the transfer of phosphate. They believe that P-enzyme first acts on amylose and mineral phosphate to give glucose-1 phosphate, which is then utilised by *iso*phosphorylase to establish 1 : 6-linkages, with the simultaneous liberation of mineral phosphate. The glucose-1 phosphate subsequently liberated by P-enzyme from the end of the original chain is used either (i) by *iso*phosphorylase to establish another branch, or (ii) by P-enzyme to lengthen the branch already established by *iso*phosphorylase.

The scheme for the conversion of amylose into amylopectin proposed by two of us in 1945 (Part I) was based on the observation that Q-enzyme functioned in the absence of both mineral phosphate and P-enzyme. The small impurities of mineral phosphate and P-enzyme known to be present in the samples of Q-enzyme then available were not regarded as being sufficient to play any part in the conversion. The publication of Bernfeld's views prompted us to examine Q-enzyme activity in greater detail, because, theoretically, a trace of mineral phosphate would be sufficient to facilitate the phosphorolytic mechanism proposed by him.

Conversion of Amylose into Amylopectin.—By treatment with Q-enzyme, linear amylose chains are transformed into the branched amylopectin structure. The evidence upon which this statement is based has been detailed in two earlier papers (Part V and *Nature*, 1948, **161**, 127). Briefly, Q-enzyme causes a rapid diminution of the absorption value, A.V. (6800 A.), of an amylose solution to about 13% of the original value. This red-staining solution contains only 2% of reducing sugar, expressed as maltose, and is hydrolysed at a higher initial rate by β-amylase than is the original amylose solution, a fact in keeping with the postulate that an increase in the number of chain-ends occurs during Q-enzyme action. When the red-staining polysaccharide produced from amylose in this manner is isolated, it is indistinguishable, in its blue value, in the light-absorption curve of its iodine-stained solution, and in its limiting conversion with β-amylase, from the purest samples of natural potato amylopectin. In this conversion, (amylose ⟶ amylopectin) equilibrium lies completely, or nearly so, on the side of the branched structure.

According to Bernfeld, *iso*phosphorylase, in the presence of P-enzyme and mineral phosphate (1·35 atoms of phosphorus per $C_6H_{10}O_5$ unit), also lowers the limit conversion with β-amylase of an amylose solution (to 65%). In this reaction, the blue-staining amylose is converted into a purple-staining polysaccharide, the latter being favoured at equilibrium. Although the polysaccharide produced in this way has not yet been isolated, it probably possesses a branched structure of the amylopectin type (Bernfeld and Meutémédian, *loc. cit.*).

It was shown in Part I that as the purification of a Q-preparation proceeded, *i.e.*, as the P-enzyme content diminished, its power to effect the synthesis of polysaccharide from glucose-1 phosphate also decreased. This has been repeatedly confirmed and in the present work quantitative experiments show that the addition of glucose-1 phosphate affects neither the rate nor the end-point of conversion of amylose into amylopectin by the purest specimens of Q-enzyme (Table III). Furthermore, the degree of branching of the product of the action of Q-enzyme on amylose is the same whether the Cori ester is present or not (Table VI).

The lack of effect of mineral phosphate on the conversion of amylose into amylopectin by Q-enzyme is shown in Table II. Two parallel digests of amylose and Q-enzyme were made in acetate buffer of pH 7 at 20°. One digest contained 0·04 atom of free-phosphorus per $C_6H_{10}O_5$ unit and the other, to which mineral phosphate was added, contained 35 times as much. Nevertheless, the rate of reaction as measured by the fall of A.V. (6800 A.) was the same in the two digests. Furthermore, the free-phosphate contents did not diminish during the reaction, which was virtually complete in 150 minutes. The same lack of effect on Q-enzyme activity was shown in a second experiment in which the mineral phosphate content was increased from 0·04 to 0·18 atom of phosphorus per $C_6H_{10}O_5$ unit.

It should be pointed out that, before any specific effect of mineral phosphate on the conversion of amylose by Q-enzyme could be ascertained, it was essential to know whether salts in general influenced the reaction. Accordingly, amylose was incubated with Q-enzyme at pH 7·0 in a series of digests which differed only with respect to concentration of citrate buffer. The rate of conversion, measured by the fall in A.V. (6800 A.), rose appreciably as the buffer concentration was increased to $4{\cdot}5 \times 10^{-3}$M. and thereafter remained constant (Table I). This marked activation of Q-enzyme by salts has also been observed by Gilbert and Swallow (in the press). It was obvious that valid conclusions concerning the effect of mineral phosphate on Q-enzyme activity could be drawn only from those experiments in which other salts were present in sufficient concentration fully to activate the enzyme.

Adopting the same method as that used in studying the effects of glucose-1 phosphate and mineral phosphate, it was demonstrated that the addition of P-enzyme does not influence the conversion of amylose by Q-enzyme, if phosphate is absent and if the enzyme is activated by the presence of other ions (see Tables IV and V).

It must therefore be concluded that the presence of a relatively large amount of mineral phosphate, of P-enzyme, or of glucose-1 phosphate does not influence the conversion of amylose into amylopectin by Q-enzyme, with respect either to rate or to type of reaction. If now Q-enzyme operates as an *iso*phosphorylase the addition of any of these three agents would be expected markedly to affect the rate of conversion as measured by the change in A.V. (6800 A.). The fact that this does not happen furnishes ample support for our view that Q-enzyme does not operate by a mechanism of phosphate transfer in the synthesis of cross-linkages.

Hehre (*J. Biol. Chem.*, **1949**, **177**, 267) has reported that an enzyme present in extracts of *Neisseria* converts crystalline corn amylose into a glycogen-like polysaccharide without the release of reducing sugars and without the addition of mineral phosphate. This enzyme would appear to have the character more of Q-enzyme than of *iso*phosphorylase.

Attention was next directed to the question of reversal of synthesis, *i.e.*, to the scission of cross-linkages and the part, if any, played by phosphate in the process. For this purpose the action of Q-enzyme on amylopectin and on the limit dextin-A was studied.

It was important in these experiments to be able to assess the degree of branching in the products of Q-enzyme activity. Such comparisons of extent of ramification were made by measuring the limit of β-amylolysis of each specimen. The smaller the proportion of branches in the substrate, the higher will be the β-amylase conversion limit. It must be borne in mind, however, that no β-amylase preparation at present available is entirely free from α-amylase and for this reason β-amylolysis must be carried out at an acid pH (usually, 4·7) at which the α-amylase is inoperative (see Peat, Whelan, and Pirt, *Nature*, **1949**, **164**, 499).

When thymol-amylopectin (blue value, B.V., 0·215) was incubated for 3 hours at pH 7·0 with fraction Q3 there was less than 1% increase in the content of reducing sugar, expressed as maltose. The polysaccharide product gave rise, by β-amylolysis at pH 4·7, to a limit dextrin and 47% of maltose, compared with 53% of maltose in the case of the parent thymol-amylopectin (Table VII). Little or no scission of the cross-links could have occurred. Indeed Q-enzyme treatment had brought about a slight increase in the degree of branching, presumably by the conversion into amylopectin of the small amylose impurity known to be present in thymol-amylopectin (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687). Identical results were obtained from a similar experiment in which mineral phosphate (1·35 atoms of phosphorus per $C_6H_{10}O_5$ unit) was introduced during the treatment of amylopectin with Q-enzyme (Table VII). It is clear that, if the synthesis of cross-links by Q-enzyme is a reversible process, then at equilibrium there is an overwhelming preponderance of the branched structure and that this equilibrium is not influenced by the presence of phosphate.

The ability of highly purified Q-enzyme (fraction Q5) to hydrolyse the cross-links of dextrin-A has been investigated (Table VIII). Although there was only a slight development of reducing power, corresponding to 1% conversion into maltose, when dextrin-A was treated for 3 hours with enzyme fraction Q5, the dextrin did become somewhat more susceptible to β-amylolysis. Whereas the original dextrin gave 2% of maltose with β-amylase, the product of Q-enzyme action gave 11·5% of maltose. It was shown once again that the presence of mineral phosphate (1·35 atoms of phosphorus per $C_6H_{10}O_5$ unit) did not materially alter the result. In this respect the action appears to be different from that of *iso*phosphorylase on the dextrin. While it is clear that slight hydrolysis, as opposed to phosphorolysis, of the dextrin had occurred during the Q-enzyme treatment, it is by no means certain that there had been a specific scission of the cross-links by Q-enzyme, for it is well-known that a very minute amount of α-amylase impurity in the enzyme sample could, by scission of 1 : 4-linkages in the " inner " polysaccharide chains, have caused the observed increase in the degree of β-amylolysis of the dextrin (Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924). We therefore note that the action of Q-enzyme on dextrin-A is not facilitated by the presence of mineral phosphate, but, until further information is available, we hestitate to attribute the action on dextrin-A to the scission of 1 : 6-linkages by Q-enzyme.

As is to be expected, whole starch behaves, in most respects, like a mixture of amylose and amylopectin under the action of Q-enzyme which simply transforms the amylose component of potato starch into amylopectin and leaves the amylopectin component essentially unchanged, so that the whole of the starch is converted into the ramified structure (Parts II and V). Q-Enzyme rapidly diminishes the viscosity of a starch paste (Parts I and VI), whereas *iso*-phosphorylase does not (*Helv. Chim. Acta*, 1948, **31**, 1724). It appears improbable that the liquefying property of Q-enzyme can be attributed to either α- or β-amylase, because (*a*) reducing sugars do not appear, (*b*) the solution never becomes achroic, and (*c*) the polysaccharide product is indistinguishable from natural amylopectin. The effect of Q-enzyme in lowering starch viscosity is not influenced by the addition of mineral phosphate (Part VI, Fig. 2).

Purity of the Q-Enzyme Preparations.—It was fully appreciated, early in this work, that the conclusions concerning the mechanism of starch synthesis and degradation depend largely on the degree of enzymic purity. In particular it was important that Q-enzyme preparations should be as free as possible from amylases. The most persistent impurity is α-amylase and tests for its presence are complicated by the doubt, which still exists, whether Q-enzyme *per se* liberates reducing groups during the conversion of amylose into amylopectin or whether this small " apparent conversion into maltose " (*ca.* 2%) is caused by a trace of α-amylase. It is certain, however, that if α-amylase is still present in the purest Q-enzyme samples, it is there in such minute quantities as not to affect the validity of the conclusions we have drawn.

In Parts IV and V of this series and also in the present paper, evidence has been presented to show that Q-enzyme, even at the Q1 stage, contains no more than a trace of either α- or β-amylase, since it effects an 87% reduction in A.V. (6800 A.) of amylose with the concomitant liberation of only 2% of reducing sugar (expressed as maltose). At this point, the solution is stained red by iodine, and does not subsequently become achroic. Fraction Q1 is free from maltase (Part IV), while fraction Q3 contains no phosphatase (no action on sodium glycerophosphate, Part VI). Fraction Q3 is normally contaminated with a little P-enzyme (Part VI), but, if during the course of its isolation it is freeze-dried at the Q1 stage in the absence of a buffer, the P-enzyme impurity is preferentially destroyed and in this way samples of fraction Q3 were obtained which were devoid of P-enzyme activity when tested by the method of Green and Stumpf (*J. Biol. Chem.*, 1942, **142**, 355).

*Synthesis of Amylopectin from Glucose-*1 *Phosphate.*—Bourne and Peat (1945) advanced the theory that P-enzyme first builds up linear polysaccharide chains by the end-wise apposition, in α-1 : 4-linkage, of glucose units derived from glucose-1 phosphate, and that these amylose-type molecules then serve as a substrate for Q-enzyme, which converts them into amylopectin in the same way as it transforms natural amylose into amylopectin. There could be no doubt that the product of the joint action of P- and of Q-enzyme on glucose-1 phosphate was amylopectin, for this synthetic polysaccharide was isolated and could not be distinguished, in its blue value, in its limit conversion with β-amylase, and in its average chain-length, as determined by end-group assay, from natural amylopectin (Part I).

Bernfeld and Meutémédian also regard the first stage in amylopectin synthesis as the formation, by P-enzyme, of linear chains. The second stage is pictured as the establishment of branch points by the addition to these chains, by *iso*phosphorylase, of single glucose units (derived from glucose-1 phosphate) in 1 : 6-linkage. It is suggested that the branches thus introduced are lengthened by subsequent P-enzyme action and in this way give rise to the " outer " chains of amylopectin. There is some doubt, however, whether the final stage in this scheme of synthesis would in fact occur, for it is known that at least three, and proably more, 1 : 4-linked glucose units must be present in an " outer " chain before the structure will serve as a template for P-enzyme (Weibull and Tiselius, *Arkiv Kemi, Min., Geol.*, 1945, **19**, *A*, No. 19). This question of the relation between structure and activating power has been discussed more fully in Part III of this series.

We have always maintained that Q-enzyme *per se* cannot utilise glucose-1 phosphate as a substrate, because increased purification of the enzyme invariably results in a decreased ability to liberate mineral phosphate from the Cori ester. Indeed this has been the method by which we have measured the progressively decreasing impurity of P-enzyme in Q-enzyme samples. Samples of Q-enzyme have now been prepared in which P-enzyme cannot be detected by the method of Green and Stumpf (*loc. cit.*), which involves incubating the enzyme sample with glucose-1 phosphate in the presence of starch and measuring the amount of mineral phosphate liberated. It follows that Q-enzyme cannot utilise glucose-1 phosphate even in the presence of the template chains furnished by starch. On the other hand, Bernfeld and Meutémédian (*loc. cit.*) demonstrated that *iso*phosphorylase does liberate mineral phosphate from the Cori ester. In this respect Q-enzyme again appears to differ from *iso*phosphorylase, but its behaviour is similar to that of Cori's branching factor from liver (*J. Biol. Chem.*, 1943, **151**, 57).

Conclusions.—The evidence presented furnishes proof that Q-enzyme does not operate by a mechanism involving phosphate, and cannot, therefore, be an *iso*phosphorylase. The conclusion appears to be inevitable that two types of enzyme are responsible for the synthesis of cross-links in branched polysaccharides, one type (*iso*phosphorylase) functioning by means of phosphate transfers and the other (Q-enzyme, Cori's " branching factor ") by a trans-glucosidase action which is independent of phosphate. It is not altogether surprising that there should be two modes of synthesis for it is well-known that starch is degraded by amylolytic as well as by phosphorolytic enzymes.

Q-Enzyme would thus be regarded as belonging, in common with other enzymes concerned in polysaccharide synthesis, to the class of trans-glycosidases, of which the phosphorylases constitute only one type (see Doudoroff, Barker, and Hassid, *J. Biol. Chem.*, 1947, **168**, 725). As discussed by us in Part V of this series, the scission of a 1 : 4-link in the amylose chain probably occurs simultaneously with the formation of a 1 : 6-link and thus appreciable quantities of short unbranched chains (" pseudo-amylose ") are not detected.

EXPERIMENTAL.

Analytical Methods.—The analytical methods employed in this work were discussed in Part IV.

Fractionation of Starch.—The amylose and amylopectin samples were isolated from potato starch by fractional precipitation of the former with thymol (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687).

Isolation of P- and Q-Enzymes from Potatoes.—Details of the method employed for the isolation of these enzymes were given in the preceding paper.

Ionic Activation of the Action of Q-Enzyme on Amylose.—Enzyme fraction Q3 was freeze-dried in the presence of citrate buffer (pH 7·0) according to the standard method described in the preceding paper. When required, the dry powder was dissolved in water (80 c.c. for each 100 c.c. of juice used in the isolation of the enzyme). This Q3 solution, which was 3·13 × 10^{-2}M. with respect to citrate buffer, was incorporated in digests containing amylose (14 mg.; B.V. 1·04), maltose (3 mg.), Q3 solution (2·0 c.c.), 0·2M-citrate buffer (pH 7·0; varying volumes), and water to make the total volume 14 c.c. in each case. The digests were incubated at 20·5° and, at intervals, aliquot portions (1 c.c. ≡ 1 mg. of amylose) were stained with iodine (2 mg.)–potassium iodide (20 mg.) in a total volume of 100 c.c. The values of A.V. (6800 A.) thus obtained were related to the concentrations of buffer employed, as is shown in Table I. In addition to these different concentrations of citrate buffer, there were other salts present in constant strength in each digest, namely sodium sulphate ($1{\cdot}12 \times 10^{-2}$M.) (arising from dissolution of the amylose in aqueous sodium hydroxide and neutralisation of the solution with sulphuric acid) and ammonium sulphate (a small residue left from precipitation of the enzyme). The Q3 fraction used in these digests had been shown, in a separate experiment, to effect a fall of 88% in the A.V. (6800 A.) of the amylose with an "apparent conversion into maltose" of only 3·0% and thus to be essentially free from the normal amylases.

TABLE I.

Ionic activation of the action of Q-enzyme on amylose.

Molarity of citrate buffer (pH 7·0) in digest ($\times 10^2$).	Fall (%) in A.V. (6800 A.) of amylose. 20 mins.	45 mins.	Molarity of citrate buffer (pH 7·0) in digest ($\times 10^2$).	Fall (%) in A.V. (6800 A.) of amylose. 20 mins.	45 mins.
0·45	40·4	61·9	3·33	51·8	69·5
1·16	47·0	65·6	4·76	53·3	69·8
1·88	48·8	66·2	6·18	54·2	69·8

When the results (Table I) were plotted it was evident that the minimum concentration of citrate buffer necessary for full activation of the enzyme was $4{\cdot}5 \times 10^{-2}$M.

Effect of Mineral Phosphate on the Rate of Conversion of Amylose by Q-Enzyme.—Fraction Q1 was dissolved in a little water and freeze-dried, a process which diminished considerably the small amount of P-enzyme impurity (see Part IV). When required, the dry powder was dissolved in water (17 c.c. for each 100 c.c. of juice used in the isolation of the enzyme). An aliquot portion (5 c.c.) of this enzyme solution was incubated at 20·5° with amylose (20 mg.; B.V. 1·30; dissolved in sodium hydroxide and neutralised with sulphuric acid, as described in Part IV), maltose (8 mg.), and M-acetate buffer (pH 7·0; 5 c.c.) in a digest having a total volume of 50 c.c. At intervals, portions (2·5 c.c. ≡ 1 mg. of amylose) were stained with iodine (2 mg.)–potassium iodide (20 mg.) in a final volume of 100 c.c. The values for % fall of A.V. (6800 A.) are shown, together with the increase in copper reducing value (expressed as maltose), in Table II. The free-phosphorus content of the digest remained constant at 0·170 mg., corresponding to 0·044 atom of phosphorus per $C_6H_{10}O_5$ unit in the amylose. This impurity of mineral phosphate had been introduced mainly with the enzyme solution.

A second digest (total volume, 50 c.c.), which was incubated simultaneously with that already described, contained, in addition to the above components, $3{\cdot}462 \times 10^{-3}$M-phosphate buffer (pH 7·0; 5 c.c.). This digest contained 0·18 atom of free phosphorus per $C_6H_{10}O_5$ unit. The values of A.V. (6800 A.) and "apparent conversion into maltose" were very similar to those recorded in the first digest (Table II).

In a second experiment with a fresh enzyme solution 1·35 atoms of free phosphorus per $C_6H_{10}O_5$ unit were added. The rate of conversion of the amylose was not increased even by this high concentration of mineral phosphate (Table II).

TABLE II.

Effect of mineral phosphate on the conversion of amylose by Q-enzyme.

Experiment.	Molarity of acetate buffer in digest.	Atoms of free phosphorus per $C_6H_{10}O_5$ unit in the amylose.	Fall (%) in A.V. (6800 A.) of amylose. 25 mins.	150 mins.	Apparent conversion into maltose (%) in 150 mins.
First	0·1	0·04	73·7	84·2	1·0
,, ...	0·1	0·18	74·0	84·3	1·2
Second	0·1	0·04	72·9	86·0	0·0
,, ...	0·1	1·39	73·0	86·4	0·0

Effect of Glucose-1 Phosphate on the Rate of Conversion of Amylose by Q-Enzyme.—Fraction Q3 was prepared from a sample of fraction Q1 which had been freeze-dried as described above. It was dissolved in water (20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzyme) and gave a solution in which phosphorylase could not be detected by the method of Green and Stumpf (*J. Biol. Chem.*, 1942, **142**, 355). This Q3 solution (4·5 c.c.) was incorporated in two digests (volume 50 c.c.) similar to those used in the previous experiment. The control digest was found to contain 0·032 mg. of free phosphorus, *i.e.*, 0·0083 atom of phosphorus per $C_6H_{10}O_5$ unit. The second digest contained the same components as the control, together with 0·1M-dipotassium glucose-1 phosphate solution (1·0 c.c.), *i.e.*, 0·81 mole of the Cori ester per $C_6H_{10}O_5$ unit. The digests were incubated at 20·5° and aliquot portions were stained with iodine in the manner described above. Glucose-1 phosphate did not influence the rate of fall of A.V. (6800 A.), as is shown in Table III.

Effect of Phosphorylase on the Rate of Conversion of Amylose by Q-Enzyme.—The enzyme fractions P2 and Q3 had been freeze-dried in citrate buffer by the standard methods described in the preceding paper. They were dissolved as required in water (20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzymes), giving solutions which contained, respectively, 14·05 and 0·78 units (Green and Stumpf) of phosphorylase per c.c. These enzyme solutions were incorporated in two digests, prepared in the usual way and having the compositions shown in Table IV. The digests were incubated at 20·5° and, at intervals, aliquot portions (1 c.c. ≡ 1 mg. of amylose) were stained with iodine as usual. As will be seen from Table V, the presence of P-enzyme did not influence the rate of fall of A.V. (6800 A.).

TABLE III.

*Effect of glucose-*1 *phosphate on the rate of conversion of amylose* (*B.V.* 1·30) *by Q-enzyme.*

Molarity of acetate buffer in digest.	Moles of Cori ester per $C_6H_{10}O_5$ unit.	Fall (%) in A.V. (6800 A.) of amylose.		
		90 mins.	105 mins.	180 mins.
0·1	Nil	71·7	73·1	78·1
0·1	0·81	71·5	72·8	77·1

TABLE IV.

Effect of P-enzyme on the rate of conversion of amylose by Q-enzyme. Composition of the digests.

	Volumes of component solutions, c.c.					
Digest.	Fraction P2.	Fraction Q3.	Amylose (B.V. 0·98) (14 mg./6·5 c.c.).	0·2M-Citrate buffer (pH 7·0).	Maltose (3 mg./1·5 c.c.).	Water.
A	Nil	1·0	6·5	1·5	1·5	3·5
B	1·0	1·0	6·5	0·5	1·5	3·5

TABLE V.

Effect of P-enzyme on the rate of conversion of amylose by Q-enzyme.

Digest.	Molarity of citrate in digest.	Units of P-enzyme (Green & Stumpf) in digest.	Fall (%) in A.V. (6800 A.) of amylose.			Apparent conversion into maltose (%).
			30 mins.	67 mins.	144 mins.	
A	$3·04 \times 10^{-2}$	0·78	68·4	76·3	83·1	2·4
B	$3·04 \times 10^{-2}$	14·83	66·3	75·7	82·9	1·8

*Effect of Glucose-*1 *Phosphate on the Degree of Branching of the Polysaccharide Produced from Amylose by Q-Enzyme.*—Fraction Q3 was prepared from a sample of fraction Q1 which had been dissolved in water and freeze-dried. The Q3 sample was dissolved in water (20 c.c. for each 100 c.c. of potato juice used in the isolation of the enzyme) and gave a solution in which phosphorylase could not be detected by the method of Green and Stumpf (*loc. cit.*). This enzyme solution (4·5 c.c.) was introduced into two of three digests, which were prepared in the usual way; all three contained amylose (20 mg.; B.V. 1·30), maltose (8 mg.), and M-acetate buffer (pH 7·0; 5 c.c., being sufficient to ensure complete ionic activation of the Q3) in a total volume of 24 c.c. A second series of three digests (24 c.c.) was prepared, each containing, in addition to the components already listed, 0·1M-dipotassium glucose-1 phosphate (1·0 c.c.), *i.e.*, 0·81 mole of the Cori ester per $C_6H_{10}O_5$ unit in the amylose. These six digests were incubated at 20·5° for different times, and N-acetic acid (5 c.c.) was then added to each; this lowered the pH to 4·7 and thus almost completely inactivated the Q-enzyme. To each digest a 0·2% solution (10 c.c.) of soya-bean β-amylase was then added, the volume adjusted to 50 c.c., and incubation continued until no further increase in reducing power occurred. The liberation of maltose was followed by means of the Shaffer–Hartmann reagent, and to the figures thus obtained small corrections were applied for the reducing powers of the orginal components of the digests. Table VI shows that the presence of glucose-1 phosphate does not influence, within the experimental error, the structure of the polysaccharide produced by Q-enzyme acting on amylose.

TABLE VI.

*Effect of glucose-*1 *phosphate on the degree of branching of the polysaccharide produced by the action of Q-enzyme on amylose.*

Fraction Q3 (free from P-enzyme) + amylose (B.V. 1·30) at pH 7·0.			β-Amylolysis of product at pH 4·7. Limit conversion into maltose (%).
Time of incubation before the addition of β-amylase (hours).	Mole of Cori ester per $C_6H_{10}O_5$ unit.	Apparent conversion into maltose (%) at end of incubation.	
0	Nil	—	89
0	0·81	—	89
1·5	Nil	—	44
1·5	0·81	—	47
3·0	Nil	1·3	40
3·0	0·81	0·0	45

Action of Q-Enzyme on the Cross-linkages of Amylopectin.—The Q3 fraction employed was the same as that used in the last experiment. Portions (4·5 c.c.) of an aqueous solution (20 c.c. for each 100 c.c. of juice used in the isolation of the enzyme) of the enzyme were introduced into three of four identical digests, which were prepared in the usual manner; all four contained amylopectin (20 mg.; B.V. 0·215), maltose (8 mg.) and M-acetate buffer (pH 7·0; 5 c.c., being sufficient fully to activate the enzyme) in a total volume of 30 c.c. A series of four similar digests (30 c.c.) was prepared, each containing, in addition to the above componets, 3·338 × 10^{-2}M-phosphate buffer (pH 7·1; 5 c.c.), *i.e.*, 1·35 atoms of free phosphorus per $C_6H_{10}O_5$ unit in the amylopectin. The eight digests were incubated at 20·5° for different periods, adjusted to pH 4·7 with acetic acid, mixed with a 0·2% solution (10 c.c.) of soya-bean β-amylase diluted to 50 c.c., and further incubated until maximum conversion into maltose had occurred. The maltose liberated was estimated by the Shaffer–Hartmann method, allowance being made for the reducing powers of the digest components.

TABLE VII.

Action of Q-enzyme on the cross-links of amylopectin.

Fraction Q3 (free from P-enzyme) + amylopectin (B.V. 0·215) at pH 7·0.			β-Amylolysis of product at pH 4·7. Limit conversion into maltose (%).
Time of incubation before the addition of β-amylase (hours).	Moles of free phosphorus per $C_6H_{10}O_5$ unit in the amylopectin.	Apparent conversion into maltose (%) at end of incubation.	
0	Nil	—	53
0	1·35	—	53
0·5	Nil	0·0	51
0·5	1·35	0·0	47
1·5	Nil	0·0	48
1·5	1·35	0·0	47
3·0	Nil	1·3	47
3·0	1·35	0·0	47

Table VII shows (i) that the Q-enzyme slightly increased the degree of branching of the "thymol"-amylopectin by an amount consistent with the conversion of the small amylose impurity in the polysaccharide into amylopectin and (ii) that the presence of mineral phosphate did not influence the conversion.

Action of Q-Enzyme on the Cross-linkages of Dextrin-A.—Fraction Q5 (see preceding paper), isolated from 100 c.c. of potato juice, was dissolved in 0·2M-citrate buffer (pH 6·5; 13 c.c.) and freeze-dried. When required, the powder was redissolved in water (100 c.c.), giving a solution which contained only 0·014 unit (Green and Stumpf) of phosphorylase per c.c.

The previous experiment was repeated using this enzyme solution with dextrin-A, prepared by β-amylolysis of thymol-amylopectin, as substrate. The results are shown in Table VIII.

TABLE VIII.

Action of Q-enzyme on the cross-links of dextrin-A.

Fraction Q5 + dextrin-A at pH 7·0.			Increase in conversion into maltose (%) during β-amylolysis at pH 4·7 for 3½ hours.
Time of incubation before the addition of β-amylase (hours).	Moles of free phosphorus per $C_6H_{10}O_5$ unit in dextrin-A.	Apparent conversion into maltose (%) at end of incubation.	
0	0	0·0	2·0
0	1·35	0·0	3·5
0·5	0	0·0	6·5
0·5	1·35	0·0	5·5
1·5	0	0·0	10·5
1·5	1·35	0·0	9·5
3·0	0	1·0	11·5
3·0	1·35	2·0	9·5

The authors are indebted to Professor M. Stacey for providing facilities for the continuation of this work in the University of Birmingham, to the Institute of Brewing for a grant to one of them (S. A. B.), and to the Colonial Products Research Council for financial assistance. They also record here their great indebtedness to Sir Norman Haworth, F.R.S., for inspiration and guidance over many years.

THE UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15.

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22. A Study of the Action of Bromine on the Silver Salts of Organic Acids.

By J. W. H. Oldham.

The action of bromine, dissolved in dry carbon tetrachloride, on the silver salts of five classes of organic acid has been investigated. (1) Monobasic aliphatic acids are decarboxylated with production of monobromides. This reaction gives a promising method of preparing *neo*pentyl halides, and is being further investigated. (2) Monobasic aromatic acids give less monobromide, and considerable quantities of the ester (formed by the loss of two atoms of silver and one molecule of carbon dioxide, from two molecules of the silver salt). (3) Monobasic aliphatic keto-acids, having the keto-group in or beyond the β-position, give about 50% of the monobromide, together with free parent acid and its bromination products. (4) Dibasic aliphatic acids give dibromides and/or lactones and bromo-acids, according to their structure. This reaction provides a method, better than any hitherto described, of obtaining alkylene dibromides where the bromine atoms are five or more carbon atoms apart. (5) Dibasic aromatic acids are sometimes unaffected by the reagent; others give some of the expected dibromide and larger quantities of the free parent acid.

For groups (1) and (2), and for some acids of group (4), the main reaction products from one or more members have been fully identified, either as known crystalline substances or, where they are oils, by conversion into known crystalline derivatives. The essentially similar analyses and properties of the products from other members of these groups point to the reactions being parallel. In group (3) and in the remaining acids of group (4) this procedure has been omitted owing to the unsatisfactory nature of the reaction. In group (5) little reaction occurred and crystalline products were recovered.

a-iso*Amyladipic* (*7-methyloctane-*1 : *4-dicarboxylic*), m. p. 67—68°, and *a*-iso*amylglutaric* (*6-methylheptane-*1 : *3-dicarboxylic*) *acid*, an oil, are described.

An earlier paper (Oldham and Ubbelohde, *J.*, 1941, 368) describes a new series of acyl derivatives of iodine prepared by the action of this halogen on the silver salts of aliphatic monobasic acids in the entire absence of water.

Although the action of bromine on the silver salts of the higher fatty acids has been studied by Mehta, Mehta, and Thosar (*J. Indian Chem. Soc.*, Indian Edn., 1940, 137) and that on the half esters of many dibasic aliphatic acids by Hunsdiecker and Hunsdiecker (*Ber.*, 1942, **75**, *B*, 291), very little has been published on the behaviour of the silver salts of aromatic or dibasic aliphatic acids. The work of the German authors on silver sebacate and adipate is in good agreement with the work described below. The behaviour of the following groups of compounds is now described: (1) monobasic aliphatic acids, (2) monobasic aromatic acids, (3) monobasic aliphatic monoketo-acids, (4) dibasic aliphatic acids, and (5) dibasic aromatic acids.

The advantages of the bromine reaction over the iodine reaction lie in the greater solubility of bromine, the greater speed of reaction, the production of fewer by-products, and the greater stability and lower boiling points of the bromo-compounds. The disadvantages are that with unsaturated acids it forms additive compounds, and with aliphatic keto-acids it has now been shown to form bromo-substituted derivatives with the consequent evolution of hydrogen bromide which, in turn, decomposes the silver salt to the original acid, causing a diminution of the yield. The choice of solvent for bromine is limited practically to carbon disulphide and carbon tetrachloride. In apparent disagreement with Hunsdiecker and Hunsdiecker (*loc. cit.*), bad yields were obtained in carbon disulphide, large quantities of the acid being recovered unchanged. Carbon tetrachloride was used throughout the present work, although the closeness of its boiling point to that of the lower alkyl bromides made the isolation of these products laborious.

It has already been shown (Oldham and Ubbelohde, *loc. cit.*) that the reaction of iodine with the silver salts of the monobasic aliphatic acids proceeds according to the equation

$$3R{\cdot}CO_2Ag + 2I_2 \longrightarrow (R{\cdot}CO_2)_3I + 3AgI \quad . \; . \; . \; . \; . \; . \; . \quad (1)$$

and that the unstable iodine acyls decompose rapidly in two ways simultaneously, the proportion of iodine present determining whether the ester, $R{\cdot}CO_2R$ (hereafter referred to as the Simonini ester), or the alkyl iodide, RI, predominate in the product:

$$(R{\cdot}CO_2)_3I \longrightarrow R{\cdot}CO_2R + RI + 2CO_2 \quad . \; . \; . \; . \; . \; . \; . \quad (2)$$

$$(R{\cdot}CO_2)_3I + I_2 \longrightarrow 3RI + 3CO_2 \quad . \; . \; . \; . \; . \; . \; . \; . \quad (3)$$

It will be seen from equation (1) that three equivalents of iodine suffice to convert all the silver present into silver iodide; if an excess of iodine is present, further reaction occurs according to equation (3).

With bromine, on the other hand, it has now been shown that the reaction cannot be stopped at stage (1), no doubt because of the very great instability of the bromine acyls which, unlike the iodine acyls usually decompose rapidly at room temperature. For compounds of shorter chain length see Birkenbach, Goubeau, and Berninger (*Ber.*, 1932, **65**, 1339) and Bockemuller and Hoffman (*Annalen*, 1935, **519**, 165) who indicate that the decomposition is even more rapid. Special experiments were carried out with silver hexoate and sebacate from which, the proportion of bromine being less than two equivalents to one of silver salt, the formation of Simonini ester would be expected according to equation (4), which summarises the equivalents of equations (1) and (2) :

$$3R{\cdot}CO_2Ag + 2Br_2 \longrightarrow R{\cdot}CO_2R + RBr + 3AgBr + 2CO_2 \quad . \quad . \quad . \quad . \quad (4)$$

Contrary to expectation, the reaction actually took place according to equation (5), which summarises the equivalents of equations (1) and (3):

$$R{\cdot}CO_2Ag + Br_2 \longrightarrow RBr + AgBr + CO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

An equivalent amount of the silver salt was recovered unchanged. As both these salts gave similar results, only the experiments with silver hexoate are described.

In spite of the precautions taken to exclude water, some of the free parent acid, as distinct from unchanged silver salt, usually appears in the products. This can be accounted for by equation (6) :

$$6R{\cdot}CO_2Ag + 3H_2O + 3Br_2 \longrightarrow 6R{\cdot}CO_2H + 5AgBr + AgBrO_3 \quad . \quad . \quad . \quad (6)$$

When the reactions were carried out under conditions of less rigorous drying, as much as 50—60% of unchanged acid was found in the product; it can readily be seen that in small-scale experiments the air in the vessel will contain as much water as in a larger-scale experiment carried out in the same vessel, and that this water will have a relatively greater effect on the reaction.

In the detailed discussion which follows, the yields given represent the average from several experiments, the results of which, while in close agreement, were never identical. The figures are percentages of the calculated theoretical yield, any unchanged silver salt having been allowed for.

Group (1). *Monobasic Aliphatic Acids.*—With silver di*iso*amylacetate (2 : 8-dimethylnonane-5-carboxylate) and *cyclo*hexanecarboxylate the actual yield of bromide was low; this may have been due to its volatility, as in these cases it was actually isolated; with the hexoate and ββ-dimethylbutyrate however, the bromide was removed, along with the solvent, on drying *in vacuo* at 100°, its yield being calculated by difference.

Group (1) *acids.*

Silver salt.	Loss of CO_2, %.	Unchanged acid, %.	Bromide, %.	Simonini ester, %.
Hexoate	91·4	5·5	92	2·4
ββ-Dimethylbutyrate	86·5	13·2	82·9	3·9
Di*iso*amylacetate	83·9	13·2	66·0	4·1
Stearate and palmitate *	93·6	5·5	89·4	0
*cyclo*Hexanecarboxylate	84·2	13·2	57·5	6·4

Equation (5) accounts for almost all the reaction of monobasic aliphatic acids (see table); when a ring is introduced, as in the *cyclo*hexanecarboxylate, more of the Simonini ester is formed, showing that reaction (4) is beginning to compete.

This reaction provides a convenient method of preparing the hitherto rather inaccessible halides of *neo*pentane, since ββ-dimethylbutyric acid is fairly easily prepared by the oxidation (best, by ozone) of di*iso*butene. In view of the importance of these compounds this is being further investigated.

Group (2). *Monobasic Aromatic Acids.*—Bromobenzene is volatile *in vacuo* at 100°, but it was isolated contaminated with less than 10% of carbon tetrachloride. The low yield of benzyl bromide may be due to its volatility *in vacuo* at 100°. The results show that here reaction (4) is competing strongly with reaction (5).

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* In cases marked thus, the principal products have been completely identified, being themselves crystallised or converted into crystalline derivatives. In other cases identity was partly inferred by analogy.

Silver salt.	Loss of CO_2, %.	Recovered acid, %.	Bromide, %.	Simonini ester, %.
Benzoate	66·1	10·6	45·8	43·9
Phenylacetate	74·5	14·0	53·7	21·0
o-Nitrobenzoate *	79·1	10·7	71·2	20·4

Group (3). *Monobasic Aliphatic Monoketo-acids.*—In this group, the reaction with bromine takes an unusual course, the greater part of the product consisting of the free parent acid, in spite of the fact that the conditions of rigorous drying were the same as in the other groups; in this reaction bromine substitution also occurs, leading to the formation of a bromo-acid. Similar results were obtained with 3-ketononane-1-carboxylic acid. With iodine on the other hand, the Simonini ester seemed to predominate in the product.

Silver salt.	Loss of CO_2, %.	Free parent acid, %.	Bromo-acid, %.	Bromide, %.	Simonini ester, %.
9-Ketodecane-1-carboxylate	42·0	50·7	4·8	39·8	Probably none

Group (4). *Dibasic Aliphatic Acids.*—If only one carboxyl group of dibasic acids is replaced by bromine, a bromo-acid results. With symmetrical acids, such as adipic, only one product, δ-bromovaleric acid can be formed; with asymmetrical acids on the other hand, such as α-methylglutaric acid, there are two possibilities: γ-bromovaleric and 4-bromobutane-2-carboxylic acid. The same considerations apply where one carboxyl group reacts with the halogen to give a lactone. Adipic acid could give only δ-valerolactone, while α-methylglutaric acid could give γ-valerolactone or α-methyl-γ-butyrolactone.

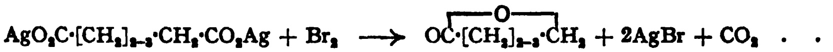
The salts in the annexed table are arranged in sub-divisions according to the distance between the carboxyl groups.

Group (4) *Acids.*

Silver salt, Sub-group A.	Loss of CO_2, %.	Dibromide, %.	Bromo-acid, %.	Lactone, %.	Free parent acid, %.
Sebacate *	94·5	81·3	7·3	0	0
Azelaäte	93·7	82·5	6·7	0	3·0
Pimelate	78·3	44·1	20·2	—	1·9
Sub-group B.					
α-*iso*Amyladipate	64·2	33·1	28·6	30·5	1·7
Adipate *	80·1	28·7	4·4	46·1	—
Sub-group C.					
α-*iso*Amylglutarate	58·7	15·8	18·6	60·5	2·8
ββ-Dimethylglutarate *	64·8	9·8	—	50·6	—
α-Methylglutarate	50·0	6·6	5·1	87·0	—
Glutarate	47·2	3·0	—	69·4	1·6
Sub-group D.					
*iso*Amylsuccinate	68·2	25·0	—	—	—
Methylsuccinate	77·0	12·6	—	—	—
Succinate	65·2	—	19·6	—	21·4
Sub-group E.					
Benzylmalonate	10—15	—	—	—	—

Sub-group A. Where the carboxyl groups are five or more carbon atoms apart the reaction is more like that of the aliphatic monobasic salts, the dibromide predominating in the product, some bromo-acid being also formed. In the case of pimelic acid some products of an ester-like type are produced which are still being investigated (see Experimental section).

Sub-group B. Here the yield of dibromide is diminished; the formation of a considerable quantity of lactone shows that, though both carboxyl groups apparently can react, the process tends to stop after one has reacted; this is even more marked in the next sub-group. In these cases, equation (4) becomes modified, and the lactone instead of the Simonini ester is formed.



$$AgO_2C\cdot[CH_2]_{2-3}\cdot CH_2\cdot CO_2Ag + Br_2 \longrightarrow \overset{\ \ \ \ \ \ \ \ \ \ O}{OC\cdot[CH_2]_{2-3}\cdot CH_2} + 2AgBr + CO_2 \quad . \quad . \quad (7)$$

Silver adipate could not be dealt with by ordinary methods as, although the neutral fraction could be obtained by extracting the reaction product with aqueous sodium hydroxide, all attempts to recover the acid resulted in extremely bad yields. The alkaline extraction method was therefore only used to determine the amount of bromo-acid present. The procedure finally adopted consisted in heating the whole of the carbon tetrachloride extract with hydrogen bromide in a sealed tube at 100°, whereupon all the lactone present was converted into the bromo-acid. The mixture could then be separated into acid and neutral fractions with a total recovery of over 95%. Both fractions were converted in good yield into their crystalline phenoxy-derivatives.

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* See footnote, p. 101.

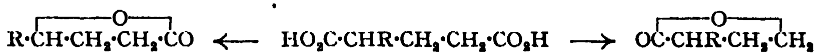
Further, silver adipate seems particularly hard to dry. On a 10-g. scale, 20—35% of the amount of adipic acid theoretically present in the original silver adipate taken was recovered from an acetone extract of the silver residues; at the same time these residues showed no appreciable oxidising power, which would be expected from equation (6). For this reason, the amount of recovered adipic acid (calculated as silver salt) has been deducted from the original weight of silver adipate when assessing the figures quoted in the table.

Sub-group C. Here the lactone is the chief product, showing that reaction (7) predominates.

Sub-group D. Here no unimolecular lactone can be formed. There is however, some evidence for the formation of di- or poly-molecular compounds of the Simonini-ester type. More dibromide is formed than in the previous group. Nearly 50% of the product was a complex mixture of acids, the nature of which has not so far been elucidated.

Sub-group E. Here the reaction appears to follow an entirely different course. Although only 10—15% of the carbon dioxide is lost, extensive bromine substitution occurs, the products being dark glasses or stiff syrups. This seems to indicate polymerisation, which most probably involves free radicals. These products darken greatly when boiled with alkali, and no definite compounds have been isolated from them.

There is little evidence in group (4) that bromine reacts with one carboxyl group in preference to the other. Because of the absence of crystalline compounds in the reaction products from the unsymmetrically substituted acids, some of the lactone from the silver α-*iso*amylglutarate reaction was converted into the amide which, if pure, would be expected to crystallise readily. The fact that the product could not be induced to crystallise seems to indicate the presence of a mixture of amides, resulting from a mixture of lactones formed by the indiscriminate reaction of both carboxyl groups as follows (R = *iso*amyl) :



$$\mathrm{R{\cdot}\overbrace{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO}^{O}} \longleftarrow \mathrm{HO_2C{\cdot}CHR{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H} \longrightarrow \mathrm{\overbrace{OC{\cdot}CHR{\cdot}CH_2{\cdot}CH_2}^{O}}$$

Group (5). *Dibasic Aromatic Acids.*—Results are recorded in the table. In the case of *iso*phthalate the figures for the loss of carbon dioxide and for dibromide refer to the small amount of product and take no account of the fact that the great bulk of the silver salt is unchanged.

Group (5). *Dibasic Aromatic Acids.*

Silver salt.	Loss of CO_2, %.	Recovered acid, %.	Dibromide, %.	Unchanged silver salt, %.
Terephthalate	—	—	—	98·0
*iso*Phthalate	25·8	—	4·0 ?	78·4
Phthalate	38·4	29·0	10·1	0

With the phthalate, silver bromide is produced quantitatively, but the dark products of the reaction consist largely of unchanged acid; there is also evidence that some bromine substitution has occurred.

EXPERIMENTAL.

General.

(Yields are expressed as weights-%, unless otherwise stated, and were determined to the nearest mg.)

Preparation of Silver Salts.—The silver salts were prepared as described previously (Oldham and Ubbelohde, *loc. cit.*), except that AnalaR sodium carbonate was used instead of ammonia solution. Analyses were within about 1% of the calculated values.

Reaction with Bromine.—Reaction was carried out in a current of rigorously dried air, previously passed through concentrated sulphuric acid, phosphoric oxide, and again concentrated sulphuric acid. A concentrated sulphuric acid trap was placed at the exit. If these precautions are not taken, 50% or more of unchanged acid is recovered.

The apparatus consists of an U-tube, one limb of which is connected directly to the air supply, the other by means of a three-way adapter to a reflux condenser which in turn is connected to the terminal sulphuric acid trap. The second limb of the adapter carries a dropping funnel, while the third is used for the air stream, which can be passed either through the U-tube or directly into the adapter, by means of a T-piece provided with taps.

The silver salt is placed in the U-tube, through which air is passed for 1½ hours, maintained at 100° in a water-bath. (Precautions must be taken against the condensation of water round the joints at the top of the U-tube.) The water-bath is then removed, and the air is caused to pass directly into the adapter by use of the appropriate taps on the T-piece. An excess over the calculated amount of a 15—18% solution of bromine in carbon tetrachloride (made up in bulk, and stored over phosphoric oxide) is added as quickly as possible through the dropping funnel, due regard being paid to the, sometimes vigorous, evolution of carbon dioxide. When the colour no longer fades, the red solution is warmed for a few minutes to ensure that the reaction is complete. Much longer boiling is sometimes necessary. The mixture is then filtered and the silver residues well washed with hot carbon tetrachloride.

Examination of the Silver Residue.—In quantitative work it is necessary to determine the amount of unchanged silver salt by extracting the silver residues with aqueous ammonia as already described (Oldham and Ubbelohde, *loc. cit.*). In the details given below the weight of silver salt recovered in this way has been allowed for.

Examination of the Product.—The filtered solution was evaporated on a water-bath and the residue usually dried *in vacuo* at 100°. In the case of the lower monobasic acids the carbon tetrachloride distillate contains the bulk of the bromo-compounds and these must be separated by distillation through a column. The procedure thereafter varied : various methods of separation were employed in each case, those recorded in the individual experiments being the most suitable. Sometimes the product was distilled; generally the neutral and the acid fraction of the product were separated by extraction three times from ether with aqueous sodium hydroxide. In the case of the higher fatty acids, alcohol must be added to this system which otherwise forms stable emulsions.

Any acids present are recovered by acidifying the alkaline extract with sulphuric acid, followed by extraction with ether; in the case of the dibasic acids it is advisable to determine any bromine in this water, since some bromo-acids produced during the reaction are decomposed by cold aqueous sodium hydroxide.

The neutral ethereal solution contains the bromides, any ester of the Simonini type, and, in the case of the dibasic acids, lactones. The product, after removal of the ether, was dried *in vacuo* at 100° and usually fractionally distilled. For the removal of lactones it was sometimes necessary to boil it with N/10-aqueous alcoholic sodium hydroxide.

Analyses.—The bromine content of the product was determined by the Stepanow method, except in the cases of the bromo-acids, for which titration with boiling N/10-alkali was usually sufficient. The carboxyl group was determined by titration with an excess of boiling N/10-alkali, followed by back-titration with N/10-nitric acid, and calculated as carbon dioxide.

Yields.—Yields quoted below for the crude products of the reaction are expressed as percentages of the weight of silver salt employed. Subsequent yields are calculated as percentages of the weight of crude product. The percentages of the theoretical yields have been given above in the tables and will not be repeated.

Details.

Group (1). *Aliphatic Monobasic Acids.*—*Special experiments with silver hexoate.* The two following experiments were designed to ascertain in what proportions bromine reacts with this salt. The quantities are expressed in g.-equivs. The calculation was complicated by the persistence of a trace of water, which gave rise to reaction (6) in which one equivalent of free parent acid is produced by one equivalent of bromine. The amount of acid present, determined by titration, must therefore be deducted from the original amount both of silver salt and of bromine. Any remaining bromine (determined by titration) or silver salt (determined as described above) must also be deducted from the original amounts. The amounts that remain then indicate the proportions in which the silver salt and the bromine have actually reacted. The determination of excess of bromine calls for no comment, but in determining the acid the carbon tetrachloride solution should be well shaken with excess of N/10-aqueous alkali, the carbon tetrachloride removed, and the excess of alkali back-titrated with acid.

(i) *Use of an excess of bromine.* 0·485 × 10^{-3} g.-equivs. of silver hexoate and 10^{-3} g.-equiv. of bromine gave 0·076 × 10^{-3} g.-equiv. of acid, 0·105 × 10^{-3} g.-equiv. remaining unchanged. Therefore the amount of silver salt used in the reaction was 0·485 − 0·076 = 0·409 × 10^{-3} g.-equiv. and that of bromine 1·000 − 0·076 − 0·105 = 0·819 × 10^{-3} g.-equiv. These figures are in the proportion of 2 : 1 and indicate that reaction (5) has indeed taken place.

(ii) *Use of an excess of silver salt.* Silver hexoate (0·612) and bromine (1·00) produced acid (0·062) (all 10^{-3} g.-equiv.), 0·081 × 10^{-3} g.-equiv. of silver salt being recovered. Therefore the amount of silver salt used is 0·612 − 0·081 − 0·062 = 0·469 and that of bromine used is 1·000 − 0·062 = 0·938 × 10^{-3} g.-equiv. These figures also are in the proportion of 2 : 1, showing that again reaction (5) has taken place.

Silver hexoate. The low yield (3·9%) shows that the bulk of the product has been removed with the carbon tetrachloride and must therefore be the bromide. Found : CO_2, 27·9% by cold titration, 31·2% by hot titration; Br, 5·8%. The cold titration corresponds to the presence of 73·6% of the free parent acid (Calc. for $C_6H_{12}O_2$: CO_2, 37·9%) and the difference between the two titrations probably indicates the presence of 13·9% of the Simonini ester (Calc. for $C_{11}H_{22}O_2$: CO_2, 23·6%). The bromine content corresponds to the presence of 10·9% of amyl bromide.

The carbon tetrachloride distillate was redistilled through a column till the temperature of the vapour reached 82°. The bromine content of the residual mixture of amyl bromide and carbon tetrachloride was 21·5%, corresponding to a 40·6% yield of amyl bromide, based on the original weight of silver salt. By calculation, a 60% yield would be expected, so presumably 33% of the product remained in the carbon tetrachloride.

Silver ββ-dimethylbutyrate. The bulk of the product (12·2% yield) consists of the bromide (Found: CO_2, 18·3% by cold titration, 21·5% by hot titration). The cold titration corresponds to the presence of 48·5% of free parent acid (Calc. for $C_6H_{12}O_2$: CO_2, 37·9%), while the difference between the two titrations probably represents 13·5% of Simonini ester (Calc. for $C_{11}H_{22}O_2$: CO_2 23·6%). The remaining 38% of the product is undoubtedly the bromo-compound, but the bromine of *neo*pentyl derivatives cannot be determined by ordinary methods. For this reason the carbon tetrachloride distillate was not further examined.

*Silver di*isoamyl*acetate.* The yield of product was 74·6% (Found : CO_2, 3·1%), of which 11·6% was a solid acid (Found : CO_2, 22·1. Calc. for $C_{12}H_{24}O_2$: CO_2, 22·0%). The neutral fraction (81·2%) gave a distillate, b. p. 85—87°/2 mm. (yield 83·4%) (Found : CO_2, 0; Br, 35·2. Calc. for $C_{11}H_{23}Br$: Br, 34·0%). The yield of residue was 12·5% (Found : CO_2, 2·2; Br, 44·0. The CO_2 content may represent 17·7% of Simonini ester. Calc. for $C_{23}H_{46}O_2$: CO_2, 12·4%).

Silver stearate. The product (78·5%) (Found : CO_2, 0·9%) gave a solid acid fraction (5·5%) (Found : CO_2, 15·4%. Calc. for $C_{18}H_{36}O_2$: CO_2, 15·4%) and a neutral fraction (93·0%), m. p. 29—30° (Found : Br, 25·7. Calc. for $C_{17}H_{35}Br$: Br, 25·0%), the residue from the evaporation of the mother-liquors having m. p. 27·8—28·2° (Found : CO_2, 0; Br, 25·1%). The m. p. of 1-bromoheptadecane is 32°.

Silver cyclo*hexanecarboxylate.* The product (65·9%, dried *in vacuo* at 60°) (Found : CO_2, 4·5%) gave a solid acid fraction (10·9%) (Found : CO_2, 34·0. Calc. for $C_7H_{12}O_2$: CO_2, 34·3%) and a neutral fraction (88·0%), which gave fractions, (i) b. p. 75—77°/2 mm. (57·3%) (Found : CO_2, 0; Br, 51·6. Calc. for $C_6H_{11}Br$: Br, 49·0%), and (ii) b. p. 70—90° (15·8%) (Found : CO_2, 6·7; Br, 31·8%. This corresponds to a mixture of 64·2% of *cyclo*hexyl bromide, calc. on the bromine, and 32·0% of the Simonini ester, calculated on the carbon dioxide values. Calc. for $C_{13}H_{22}O_2$: CO_2, 20·9%). The residue (4·4%) was a black tar. The loss in weight in this distillation is probably due to the volatility of *cyclo*hexyl bromide.

Group (2). *Aromatic Monobasic Acids.—Silver benzoate.* The yield of product (Found : CO_2, 20·1%) was 32·0%. As phenyl benzoate is very unstable to alkalis the ethereal solution of the product was extracted with aqueous potassium hydrogen carbonate and gave a crystalline acid fraction (27·2%) (Found : CO_2, 30·9. Calc. for $C_7H_6O_2$: CO_2, 36·0%). The low value for CO_2 indicates the presence of 14·2% of non-acidic material, probably phenol, which in turn would represent 30·1% of phenyl benzoate which has been hydrolysed even under these mild conditions. The neutral fraction (66·9%) was partly solid (Found : CO_2, 17·0%. This indicates the presence of 76·5% of phenyl benzoate. Calc. for $C_{13}H_{10}O_2$: CO_2, 22·2%), the rest being probably bromobenzene. The carbon tetrachloride distillate was distilled through a column till the temperature of the vapour reached 81°. The amount of carbon tetrachloride remaining in the residue was 8·3% (Found : Br, 46·7%) making the yield of bromobenzene 26·1% of the original silver benzoate.

Silver phenylacetate. The product (57·9%) (Found : CO_2, 7·9; Br, 30·5%) gave a solid acid fraction (14·4%) (Found : CO_2, 30·6. Calc. for $C_8H_8O_2$: CO_2, 32·3%) and a neutral fraction (81·0%), yielding fractions, (i) b. p. 73—80°/2 mm. (60·0%) (Found : CO_2, 0·8; Br, 44·9%. The CO_2 content indicates the presence of 4·1% of the Simonini ester. Calc. for $C_{15}H_{14}O_2$: CO_2, 19·4%. Calculation on the bromine content gives 96·1% of benzyl bromide. Calc. for C_7H_7Br : Br, 46·7%), and (ii) b. p. 80—130°/2 mm. (31·9%) (Found : CO_2, 9·6; Br, 23·2%. This corresponds to a mixture of 49·4% of the Simonini ester, calculated on the CO_2, and 49·9% of benzyl bromide, calculated on the bromine content). The loss in weight may be due to the volatility of benzyl bromide.

Silver o-*nitrobenzoate.* The product (70·4%) gave a solid acid fraction (9·3%) (Found : CO_2, 25·0. Calc. for $C_7H_5O_4N$: CO_2, 26·3%) and a crystalline neutral fraction (89·4%) (Found : CO_2, 2·6; Br, 32·9%). These figures correspond to a mixture of 83·0% of *o*-bromonitrobenzene (m. p. 41·5°) (Calc. for $C_6H_4O_2NBr$: Br, 39·6%) and 17·0% of the Simonini ester (Calc. for $C_{13}H_8O_6N_2$: CO_2, 15·2%). The substance softened at 32° and melted at 37—40°.

Group (3). *Aliphatic Monobasic Monoketo-acids.—Silver* 9-*ketodecane*-1-*carboxylate.* The product (72·1%) (Found : CO_2, 11·5; Br, 19·5%) was extracted from ether with sodium carbonate solution to give a largely solid acid fraction (47·3%) (Found : CO_2, 21·0; Br, 3·7%). This corresponds to a mixture of 87·1% of the free parent acid (Calc. for $C_{11}H_{20}O_3$: CO_2, 22·0%) with 12·9% of its monobromo-derivative (Calc. for $C_{11}H_{19}O_3Br$: CO_2, 15·7; Br, 28·6%), calculated from the bromine content; or 84·2 and 15·8% respectively calculated from the CO_2 content. For the neutral fraction (46·9%) (Found : CO_2, 2·5; Br, 30·7%) the bromine content corresponds to the presence of 90·3% of the bromo-compound (Calc. for $C_{10}H_{17}OBr$: Br, 34·0%).

Group (4). *Silver Salts of the Aliphatic Dibasic Acids.*—In this group, the acid fraction is usually a mixture of the free parent acid and bromo-acid. The composition of the mixture was calculated from the CO_2 content, and also from the bromine content. In all cases these agreed within 3%, and the average value is given below.

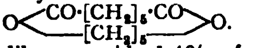
Sub-group A. (i) *Silver sebacate.* The yield of product was 61·3%. A further 0·9% was obtained by extracting the silver residues with acetone, and this material, crystallised from acetone, had m. p. 108—118° (Found : CO_2, 27·7; Br, 2·3%); the nature of this substance, more of which was obtained from the main fraction, remains obscure. The acid fraction (8·6%) (Found : CO_2, 16·2; Br, 31·7%), on treatment with light petroleum, gave 7·9% of a white crystalline substance, m. p. 118—120° (Found : CO_2, 33·7; Br, 0%). This was doubtless the same as the product from the acetone extract described above. An oil (91·7%) obtained on removal of the light petroleum was dissolved in ether and again extracted with aqueous sodium hydroxide; 8·7% was obtained from the ether and was added to the main neutral fraction; 86·1% of an acid product was isolated which crystallised (m. p. 31—33°) and was so soluble in all solvents that recrystallisation was unsatisfactory [Found : CO_2, 17·2; Br, 31·8%. Calc. for 9-bromopelargonic acid (m. p. 36—36·5°), $C_9H_{17}O_2Br$: CO_2, 18·5; Br, 33·7%]. The neutral fraction (90·2%) gave a distillate (94·8%), b. p. 140°/5 mm. (Found : CO_2, 0; Br, 59·3. Calc. for $C_8H_{16}Br_2$: Br, 58·8%). The dark residue (4·7%) (Found : CO_2, 5·7; Br, 44·5%) was not further examined. The products of the reaction contained 85·4% of the dibromide, 6·7% of the bromo-acid, 2·1% of an unknown crystalline acid, and 4·2% of a dark residue.

The distillate was treated with sodium phenoxide as described by Ssolonina (*Zentr.*, 1899, I, 26), giving a 99% yield of the diphenoxy-derivative, m. p. (after recrystallisation from absolute alcohol) 84—86° (lit., 83—84°), while 8·1% of impure crystals, m. p. 44—51°. were obtained from the mother-liquors.

(ii) *Silver azelaäte.* The product (64·2%) gave an acid fraction (8·0%) (Found : CO_2, 26·7; Br, 25·6%). This corresponds to a mixture of 72·8% of the bromo-acid (Calc. for $C_8H_{15}O_2Br$: CO_2, 19·7; Br, 35·8%) and 27·2% of azelaic acid (Calc. for $C_9H_{16}O_4$: CO_2, 46·8%) and a neutral fraction (91·7%) which gave a distillate (89·9%), b. p. 125°/2 mm. (Found : CO_2, 0; Br, 61·0. Calc. for $C_7H_{14}Br_2$:

Br, 62·0%). The residue (7·3%) was not further investigated. The products contained 82·4% of the dibromide, 5·8% of the bromo-acid, and 2·2% of azelaic acid.

(iii) *Silver pimelate.* The product (59·3%) (Found : CO_2, 8·6%) give an acid fraction (19·2%) [Found : CO_2, 24·3; Br, 37·7. This corresponds to a mixture of 92·9% of the bromo-acid (Calc. for $C_6H_{11}O_2Br$: CO_2, 22·5 Br, 41·0%) and 7·1% of pimelic acid (Calc. for $C_7H_{12}O_4$: CO_2, 55·0%)]. The neutral fraction (72·2%) gave a distillate, b. p. 120°/2 mm. (63·4%) (Found : CO_2, 0; Br, 71·5. Mainly $C_5H_{10}Br_2$: Calc., Br, 69·9%). The residue (35·5%) was boiled with aqueous alcoholic sodium hydroxide but no very clear-cut results were obtained; the isolation of 8·5% of a neutral substance would seem to indicate the presence of a compound of the type of a Simonini ester, formed by the unsymmetrical loss of two molecules of CO_2 between two molecules of pimelic acid, such as



$O<\begin{matrix}CO\cdot[CH_2]_5\cdot CO\\ [CH_2]_5\end{matrix}>O$. The product of the reaction contained 45·8% of the dibromide, 17·8% of the dibromo-acid, 1·4% of free parent acid, and 25·6% of an unknown substance which is being further investigated.

Sub-group B. (i) *Silver* α-iso*amyladipate.* The product (54·2%) (Found : CO_2, 13·5%) gave a distillate, b. p. 115—130°/2 mm. (44·1%). The CO_2 content (2·0%) corresponds to the presence of 7·4% of the lactone (Calc. for $C_{10}H_{18}O_2$: CO_2, 25·8%); allowing for this, the bromine content (53·9%) is revalued at 58·3%, showing that the substance is mostly the dibromide (Calc. for $C_9H_{18}Br_2$: Br, 55·8%). The residue (53·0%) (Found : CO_2, 21·7 Br, 17·6%) corresponds to a mixture of 55·3% of the bromo-acid) (Calc. for $C_{10}H_{19}O_2Br$: CO_2, 17·5; Br, 31·8%), 41·7% of the lactone, and 3% of *iso*amyladipic acid (Calc. for $C_{11}H_{20}O_4$: CO_2, 40·7%). In this case also the residue was boiled with excess of alkali, giving results similar to those described for pimelic acid; the isolation of 13·2% of a neutral substance indicates the presence of a compound of the Simonini ester type. The reaction products contained 40·7% of the dibromide, 29·3% of the bromo-acid, 1·6% of *iso*amyladipic acid, and 22·1% of lactone + Simonini-like compound. This is being further investigated

(ii) *Silver adipate.* (*a*) The yield obtained in carbon tetrachloride was 29·5% (Found : CO_2, 16·4%). The silver residues were extracted with hot acetone, giving a further 11·9% of crystalline product (cf. p. 103) (Found : CO_2, 55·3%), softening at 136°, m. p. 141—146°, unchanged on admixture with adipic acid. As it remained impure after recrystallisation from glacial acetic acid, it was converted into the ethyl ester and distilled (88·5% yield) (Found : CO_2, 43·6. Calc. for $C_{10}H_{18}O_4$: CO_2, 43·5%). The residue was a dark gum. The ester was hydrolysed to adipic acid (99·5%) (Found : CO_2, 59·2. Calc. for $C_6H_{10}O_4$: CO_2, 60·2%), m. p. 151—153°, unchanged on mixing with adipic acid. Allowance being made for this amount of adipic acid, the yield of other products in the carbon tetrachloride extract is 40·1%.

Although the neutral portion of the usual alkaline extraction could be isolated without difficulty, it proved impossible to isolate the acid portion in good yield. The amount of bromo-acid present was determined by boiling the strongly alkaline extract for ½ hour and determining the bromine content. This was equivalent to the presence of 5·7% of the bromo-acid in the original carbon tetrachloride extract.

(*b*) The crude product from the carbon tetrachloride was heated in a sealed tube for 2 hours at 100° with four times the theoretical amount of hydrogen bromide in glacial acetic acid and an excess of acetic anhydride to destroy any water present; the product was evaporated to dryness *in vacuo* at 100°. As the dibromide is considerably volatile under these conditions, the total distillate was flooded with water, neutralised with sodium carbonate, and extracted with ether, comparatively large quantities of the dibromide being recovered. The total yield of product was 130·4%. The alkaline extract thereof (all solutions were kept ice-cold) was immediately run into ice-cold acid. The acid fraction (52·1%) (Found : CO_2, 25·8; Br, 44·3. Calc. for $C_5H_9O_2Br$: CO_2, 24·3; Br, 44·2%) failed to crystallise, and its subsequent identification is described below. The neutral fraction (45·2%) gave a distillate (71·8%), b. p. 80—90°/5 mm. Analysis (CO_2, 13·3; Br, 5·4%) of the residue (24·2%) might indicate presence of 4-bromobutyl δ-bromovalerate (Calc. for $C_9H_{16}O_2Br_2$: CO_2, 13·6; Br, 50·0%); this substance would easily have distilled under the conditions employed. As this material represented only 12—15% of the reaction product, it was not further investigated. The bulked distillates from several experiments were redistilled (yield 93·7%), b. p. 75—85°/5 mm. (Found : CO_2, 0; Br, 71·3. Calc. for $C_4H_8Br_2$: Br, 74·0%), a residue (3·3%) (Found : Br, 31·0%) not being further investigated.

The products of the reaction contained 31·1% of the dibromide, 28·7% of adipic acid, 22·8% of the lactone, 4·0% of the bromo-acid, and 10·1% of unidentified material. If the carbon tetrachloride extract only is considered, these figures become 42·3, 32·0, 5·7, and 14·2%, respectively.

The distillate was converted into 1 : 4-diphenoxybutane as described above (yield 92·0% of theory). Recrystallisation from absolute alcohol yielded crystals, m. p. 99—100° (lit., 99°). The mother-liquors yielded 15·0% of material, m. p. 30—40°.

The bromo-acid was heated with twice its volume of thionyl chloride on a water-bath, and then treated cautiously with a small quantity of alcohol, evaporated to dryness *in vacuo* at 100° (yield 99·3%) (Found : CO_2, 22·9; Br, 33·7. Calc. for $C_7H_{13}O_2Br$: CO_2, 22·1; Br, 38·2%), and distilled (distillate : 71·7%; b. p. 100—105°/5 mm.; residue : 7·6% of a black tar). As treatment of the ester with sodium phenoxide in alcohol gave a very poor yield of the acid (presumably owing to the formation of δ-valerolactone), it was boiled in acetone with the acetone compound of sodium phenoxide (Segaller, *J.*, 1914, **105**, 112). Two treatments with this reagent removed the bromine completely. In this case hydrolysis also occurred, the acid, and no δ-valerolactone being formed. Ethyl δ-phenoxyvalerate (59·9% of theory) (Found : CO_2, 18·9; Br, 0. Calc. for $C_{13}H_{18}O_3$: CO_2, 19·8%) was isolated by removing the acetone on a water-bath, shaking the residue with water–ether, and washing the ethereal layer with sodium hydroxide solution. This was hydrolysed with aqueous-alcoholic sodium hydroxide and, as the solution became cloudy on removal of the alcohol, it was extracted with ether, from which 5·2% of a neutral crystalline compound was obtained in insufficient quantity for further work. The solution was then acidified and extracted with ether, yielding 96·1% of the calculated amount of δ-phenoxyvaleric acid (after allowance for the neutral substance mentioned above), m. p. 62—63°.

The substance was too soluble in all solvents to be satisfactorily recrystallised, but on being pressed between filter paper had m. p. 63—65° (lit., 66°) (Found : CO_2, 21·9. Calc. for $C_{11}H_{14}O_3$: CO_2, 22·6%). More acid (impure) was recovered from the alkaline washings from the ester; these were bulked, acidified, neutralised with potassium hydrogen carbonate solution, extracted 3 times with ether to remove phenol, again acidified, and extracted with ether. The yield of impure dark acid was 32·4%, making the total yield 93·3% of theory (Found : CO_2, 20·8%).

The bromo-ester was treated with excess of ethyl sodiomalonate, hydrolysed by alkali, decarboxylated at 180—200°, and dried *in vacuo* at 100°. This gave 81·0% of pimelic acid, m. p. 101—104° (after recrystallisation from benzene) (Found : CO_2, 53·4. Calc. for $C_7H_{12}O_4$: CO_2, 55·0%), unchanged on mixing with an authentic specimen. The mother-liquors yielded 36·0% of impure product. The somewhat unsatisfactory yield of pimelic acid is a feature common to many decarboxylations of malonic derivatives.

Sub-group C. (i) *Silver γ-*iso*amylglutarate.* The product (45·9%) (Found : CO_2, 19·0; Br, 24·6%) gave a distillate, b. p. 110—120°/2 mm. (67·9%) (Found : CO_2, 2·3% by cold titration, 17·6% by hot titration; titratable Br, 4·2%; total Br, 25·1%). The bromine content by titration agrees with the CO_2 content by cold titration to indicate the presence of 12·4% of the bromo-acid (Calc. for $C_9H_{17}O_2Br$: CO_2, 18·5; Br, 33·7%). The remaining 15·3% of CO_2 corresponds to 54·2% of the lactone (Calc. for $C_9H_{16}O_2$: CO_2, 28·2%). With allowance for these factors the bromine content of the remainder is revalued at 62·7% (Calc. for $C_8H_{16}Br_2$: Br, 58·8%). Analysis (CO_2, 26·6; Br, 16·8%) of the residue (29·1%) corresponds to a mixture of 49·9% of the bromo-acid, 26·6% of the lactone, and 23·6% of α-*iso*amylglutaric acid (Calc. for $C_{10}H_{18}O_4$: CO_2, 43·5%). To confirm this the residue was boiled with excess of alkali, whereupon it gave 11·8% of a neutral substance, which was not further examined, 16·8% of bromine, and 69·4% of an acid (Found : CO_2, 32·6%), corresponding to a mixture of 71·3% of the lactone and 28·7% of *iso*amylglutaric acid. The expected amount of α-*iso*amylglutaric acid was only 11·8%, but the neutral material could correspond to a further 15·9% of this acid. The reaction products consisted of 22·6% of the dibromide, 22·9% of the bromo-acid, 49·5% of the lactone, and 2·8% of *iso*amylglutaric acid.

(ii) *Silver ββ-dimethylglutarate.* The product (29·2%) (Found : CO_2, 28·4; Br, 15·1%) was boiled with a slight excess of N/10-aqueous-alcoholic sodium hydroxide, giving a neutral fraction (21·6%) (Found : CO_2, 1·4; Br, 65·7%), the CO_2 content of which corresponds to the presence of 3·6% of the lactone (Calc. for $C_6H_{10}O_2$: CO_2, 38·5%). With allowance for this, the bromine content of the remainder becomes 68·2% (Calc. for $C_5H_{10}Br_2$: Br, 69·9%). The acid fraction (61·5%) [Found : CO_2, 39·4%. The aqueous portion contained 11·4% of bromine which corresponds to 27·8% of the bromo-acid (Calc. for $C_6H_{11}O_2Br$: CO_2, 22·5; Br, 41·0%)] gave a distillate, b. p. 80°/2 mm. (84·5%) (Found : CO_2, 38·4%). In spite of its good analysis the distillate crystallised badly, and a cold titration showed CO_2, 1·3%. The *residue* was 11·2% (Found : CO_2, 52·5. Calc. for ββ-dimethylglutaric acid, $C_7H_{12}O_4$: CO_2, 55·0%). The reaction products consisted of 20·8% of the dibromide, 27·8% of the bromo-acid, 36·5% of the lactone, and 6·8% of ββ-dimethylglutaric acid.

(iii) *Silver α-methylglutarate.* The product (31·7%) (Found : CO_2, 38·5%) gave a distillate, b. p. 65—80°/2 mm. (76·3%) [Found : CO_2, 36·7; Br, 12·0%. This corresponds to a mixture of 83·6% of the lactone (Calc. for $C_5H_8O_2$: CO_2, 44·0%) and 16·4% of the bromo-compound (Calc. for $C_4H_8Br_2$: Br, 74·0%). The bromine content (17·7%) of the residue (21·7%) (Found : CO_2, 34·6%) indicates the presence of 40% of the bromo-acid (Calc. for $C_5H_9O_2Br$: CO_2, 24·3; Br, 44·2%) with 60% of the lactone, but such a mixture would require CO_2, 36·1%. The reaction products consisted of 12·5% of the dibromide, 8·2% of the bromo-acid, and 76·1% of the lactone.

(iv) *Silver glutarate.* There was no evidence of the presence of trimethylene bromide. The product (24·4%) gave a distillate, b. p. 70—80°/2 mm. (54·0%) (Found : CO_2, 44·4; Br, 10·9%). These values indicate a mixture of 83·6% of the lactone (Calc. for $C_4H_6O_2$: CO_2, 51·1%) and 16·4% of the dibromide (Calc. for $C_3H_6Br_2$: Br, 79·2%). They do not agree so well with any mixture containing the bromo-acid. The residue (36·4%) (Found : CO_2, 52·2; Br, 0%) is a mixture of the lactone and 7·0% of glutaric acid (Calc. for $C_5H_8O_4$: CO_2, 66·6%). The reaction product consisted of 7·2% of the dibromide, 70·6% of the lactone, and 2·6% of glutaric acid. The deficiency shown by these figures is possibly due to the loss of the volatile dibromide.

Sub group D. (i) *Silver* iso*amylsuccinate.* The product (50·7%) (Found : CO_2, 13·7; Br, 35·0%) gave a neutral fraction (71·0%) (Found : CO_2, 7·1; Br, 44·6%), b. p. 85—95°/2 mm. (63·7%) (Found : CO_2, 4·3; Br, 55·4%), and a residue (35·0%) (Found : CO_2, 11·0; Br, 26·6%), presumably consisting of products of the Simonini-ester type. The CO_2 content of the distillate indicated the presence of an ester, a lactone being impossible. The distillate was therefore boiled with aqueous-alcoholic N/10-sodium hydroxide, to give 70·2% of a neutral material [Found : CO_2, 0·8; Br, 61·0. Mostly dibromide (Calc. for $C_7H_{16}Br_2$: Br, 62·0%)] and 12·1% of an acid (Found : CO_2, 24·5%). The residual aqueous solution contained 6·5% of bromine. The CO_2 content of the acid could correspond to that required by a dihydroxy-acid (Calc. for $C_8H_{16}O_4$: CO_2, 25·0%). To confirm this it was treated with silver oxide and ethyl iodide, but it gained only 11·2% in weight. The CO_2 content however proved to be 17·3% which is close to that required by the ethyl ester of a diethoxy-acid (Calc. for $C_{14}H_{28}O_4$: CO_2, 16·9%). The acid fraction (26·9%) (Found : CO_2, 24·1; Br, 17·7%) was a complex mixture from which no definite product could be isolated. The products of the reaction contained 31·7% of the dibromo-compound.

(ii) *Silver methylsuccinate.* No dibromide could be found in the carbon tetrachloride distillate. The product (28·5%) (Found : CO_2, 20·5%) gave a neutral fraction (60·0%) (Found : CO_2, 14·5; Br, 57·3%), b. p. 110—115°/2 mm. (58·3%) (Found : CO_2, 7·9; Br, 58·8%), probably mostly the dibromide (Calc. for $C_3H_6Br_2$: Br, 79·2%) mixed with an acidic substance of similar nature to that obtained from silver *iso*amylsuccinate. The residue (40·0%) (Found : CO_2, 17·7; Br, 50·1%) was not further investigated. The acid fraction (36·5%) was a complex mixture from which no definite product could be isolated. The reaction products contained a maximum of 26·0% of the dibromo-compound, which would be lowered if the ester in the neutral fraction itself contained bromine. The rest of the product was indefinite.

(iii) *Silver succinate.* The reaction mixture required 1½ hours' boiling. Fractionation of the carbon tetrachloride disclosed no ethylene dibromide. Dissolution of the product (20·2% yield) (Found: CO_2, 45·9%) in ether gave 37·7% of succinic acid (Found : CO_2, 74·6. Calc. for $C_4H_6O_4$: CO_2, 74·5%). The material (61·0%) (Found : CO_2, 32·8; Br, 39·1%) from the ethereal solution was again dissolved in ether, the solution was washed 3 times with water, and the washings were extracted with ether. Titration of the water showed CO_2, 40·3. 89% of material (Found: CO_2, 30·9; Br, 43·1%) was recovered from the ether. The bromine content corresponds to the presence of 82·5% of the bromo-acid (Calc. for $C_3H_5O_2Br$: CO_2, 28·7; Br, 52·2%), and 17·5% of a substance containing CO_2, 41·1%. The nature of the latter, as of the substance in the water, remains obscure. The reaction product contains 44·8% of bromo-acid, and 37·7% of succinic acid.

Sub-group E. (i) *Silver benzylmalonate.* The reaction mixture was boiled for ½ hour, and the silver residue well washed with hot carbon tetrachloride and then hot acetone. The carbon tetrachloride solution yielded 14·9% of a stiff syrup (Found: CO_2, 21·1; titratable Br, 31·6%). The yield of product from the acetone was 64·2% (Found : CO_2, 24·6°; titratable Br, 27·4; total Br, 38·1%); it was a glass, insoluble in ether. The analysis shows that only 12·0% of " CO_2 " content had been lost, and that extensive bromination had occurred, some of the bromine having apparently even entered the ring. Treatment with alkali caused great darkening, even in the cold, and nothing but dark syrups or glasses could be isolated.

Group (5). *Aromatic Dibasic Acids.—Silver terephthalate.* The reaction mixture was boiled for 3 hours with occasional addition of more bromine. Examination of the silver residues by standard methods showed the presence of only 2·0% of silver bromide, 98·0% of the silver salt being recovered unchanged. Analysis of the product (5·8%) showed CO_2, 19·2%. Bromobenzoic acid $C_7H_5O_2Br$ requires CO_2, 21·8%, but as the product did not crystallise there can have been none of this acid present. There was too little product for further investigation.

Silver iso*phthalate.* The mixture was boiled for 3 hours. The silver residues were extracted with hot acetone in addition to carbon tetrachloride. The yield from both extracts was 13·6% (Found : CO_2, 26·8%). The neutral fraction (18·3%) was not further examined, but was probably the dibromide. The acid fraction (80·3%) (Found : CO_2, 36·0%), m. p. >300°, was boiled with benzene, in which *iso*phthalic acid is insoluble, and filtered. The crystalline residue (Found : CO_2, 52·0. Calc. for $C_8H_6O_4$: CO_2, 55·0%), was not further examined. Analysis of the silver residues indicated the presence of 21·6% of silver bromide, showing that 78·4% of the salt was unchanged. The reaction products appeared to consist of 37·7% of *iso*phthalic acid and 15·7% of a neutral substance, probably the dibromide, the rest of the product being unidentified.

Silver phthalate. The mixture was boiled for ½ hour. The carbon tetrachloride gave 34·7% of material (Found : CO_2, 25·7%). A further 12·6% were obtained by extracting the silver residues with hot acetone (Found : CO_2, 44·9%), this being dark and having m. p. 190—200°, unchanged by admixture with phthalic acid (Calc. for $C_8H_6O_4$: CO_2, 53·0%). The main product was extracted from ether with aqueous sodium hydroxide, leaving a neutral fraction (18·2%) (Found : CO_2, 0; Br, 62·6. Calc. for $C_6H_4Br_2$: Br, 68·3%). The dark acid fraction (80·9%) (Found : CO_2, 30·9%) was purified by treatment with silver oxide and ethyl iodide, to give an ester, b. p. 155—170°/2 mm. (88·7%) (Found : CO_2, 20·3 ; Br, 12·9%). The residual black tar was not further examined. The distillate was hydrolysed and the acidified solution (*A*) extracted with chloroform, in which phthalic acid is insoluble; the yield of partly crystalline product was 27·7% (Found: CO_2, 15·7%). Dibromobenzoic acid (Calc. for $C_8H_3O_2Br_2$: CO_2, 15·1%) is a strongly crystalline substance. Further extraction of (*A*) with ether yielded an oil (49·1%) (Found : CO_2, 39·9%), which when rubbed with chloroform afforded phthalic acid (m. p. and mixed m. p.); 62·4% of the ether-extracted material was recovered from the chloroform mother-liquors (Found : CO_2, 27·3%). This reaction gave 13·3% of the dibromide, 26·8% of phthalic acid, and a number of unidentified acidic products.

Note on the Purity of the Acids used.—Azelaic acid was made from Kahlbaum's monomethyl azelaāte; stearic and palmitic acids were Kahlbaum's and Schuchardt's respectively. The following were pure commercial products : hexoic, benzoic, nitrobenzoic, phenylacetic, phthalic, *iso*phthalic, terephthalic, adipic, and succinic acid. The sebacic acid, being coloured, was recrystallised once from glacial acetic acid. The keto-acids were made by Ruzicka and Stoll's method (*Helv. Chim. Acta*, 1927, **10**, 691). The other acids were made from ethyl malonate.

*γ-*iso*Amyladipic acid.* Ethyl sodiomalonate was treated successively with ethyl γ-bromobutyrate (from ethyl sodiomalonate and 2-phenoxyethyl bromide) and *iso*amyl bromide, and the product then hydrolysed, decarboxylated, and purified by re-esterification and distillation (Found : CO_2, 40·8. Calc. for $C_{11}H_{20}O_4$: CO_2, 40·7%); it had m. p. 66—68° and gave a silver salt (Found : Ag, 50·1. Calc. for $C_{11}H_{18}O_4Ag_2$: Ag, 50·2%).

*α-*iso*Amylglutaric acid.* Ethyl sodiomalonate was treated successively with ethyl β-bromopropionate and *iso*amyl bromide; the product, isolated as above, failed to crystallise, even on long storage (Found : CO_2, 43·4. Calc. for $C_{10}H_{18}O_4$: CO_2, 43·5%). The silver salt was also analysed (Found : Ag, 51·0. Calc. for $C_{10}H_{16}O_4Ag_2$: Ag, 51·9%).

Thanks are due to the Managers of the Royal Institution for the facilities provided during the research, to Professor Rideal for his continued interest and encouragement, and to Professor Ubbelohde for kindly criticism.

THE ROYAL INSTITUTION,
ALBEMARLE ST., LONDON, W.1.

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23. *Chemotherapeutic Diamidines. The Sulphur Analogue of 4 : 4'-Diamidinostilbene.*

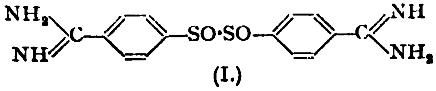
By Ludwig Bauer and J. Cymerman.

Preparation of di-*p*-cyanophenyl disulphoxide (III) is described. Attempts to synthesise di-*p*-amidinophenyl disulphoxide (I), a sulphur analogue of 4 : 4'-diamidinostilbene, by interaction of (III) with ammonium thiocyanate, ammonium benzenesulphonate, and ammonium benzenesulphonate and ammonia gave, in every case, di-*p*-amidinophenyl disulphide, which has been prepared also by interaction of di-*p*-cyanophenyl disulphide with ammonium thiocyanate and by the Pinner method by way of the 4 : 4'-*di*(*carboxyimino ethyl ether*) *dihydrochloride*. Application of the Pinner method to (III) gave its 4 : 4'-*di*(*carboxyimino ethyl ether*) but alcoholic ammonia yielded only the disulphide diamidine. Reaction mechanisms are discussed. Heating the di-imino diethyl ether dihydrochlorides afforded the corresponding diamides; 4 : 4'-*di*-(p-N-*phenylamidinophenyl*) *disulphide dibenzenesulphonate* was prepared, but attempted preparation of the disulphoxide analogue from (III) gave a deep-blue compound of unknown structure. Ultra-violet absorption spectra of aromatic disulphides and disulphoxides have been determined.

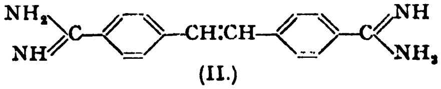
The chemotherapeutic properties of diamidines are well known (Lourie and Yorke, *Ann. Trop. Med. Parasit.*, 1937, **31**, 435; 1939, **33**, 289; King, Lourie, and Yorke, *Lancet*, 1937, **233**, 136), the aromatic diamidines, in particular, showing pronounced antibacterial activity (Ashley, Barber, Ewins, Newbery and Self, *J.*, 1942, 103; Wien, *Brit. J. Pharmacol.*, 1948, **3**, 211). Replacement of carbon by sulphur in many organic compounds of biological interest has yielded sulphur analogues of lower toxicity and equal or increased activity (Steinkopf and Ohse, *Annalen*, 1924, **437**, 14; 1926, **448**, 205; Warren, Marsh, Thompson, Shelton, and Becker, *J. Pharm. Exp. Therap.*, 1943, **79**, 187; Dann and Moller, *Ber.*, 1947, **80**, 23) and it was thus of interest to attempt the synthesis of di-*p*-amidinophenyl disulphoxide (I), a sulphur analogue of 4 : 4'-diamidinostilbene (II) which has outstanding trypanocidal activity (Ashley *et al.*, *loc. cit.*).

The required starting material, di-*p*-cyanophenyl disulphoxide (III), was obtained by Cymerman, Koebner, and Short (*J.*, 1948, 381) in low yield as a by-product in the preparation of *p*-cyanobenzenesulphinic acid. Its attempted preparation from the sulphinic acid at 80—90° in the presence of hydriodic acid and sulphur dioxide (Otto, *Ber.*, 1882, **15**, 121; Smiles and Gibson, *J.*, 1924, 180; von Braun and Weissbach, *Ber.*, 1930, **63**, 2836; Hilditch, *J.*, 1910, 1096) gave only an acidic hydrolysis product, presumably di-*p*-carboxyphenyl disulphoxide, in 90% yield, while the action of concentrated hydrochloric acid on the sulphinic acid at 25° for 3 days yielded the disulphoxide (55%) accompanied by the corresponding diamide. However, hydrochloric acid at 0° during 2—3 days readily afforded 70% of pure (III); the mother-liquors contained *p*-cyanobenzenesulphonic acid, isolated as the p-*toluidine* salt in 45% yield, in agreement with the accepted mechanism (1) for the formation of disulphoxides from the sulphinic acids (Otto, *Ber.*, 1876, **9**, 1639; Pauly and Otto, *ibid.*, 1877, **10**, 2181; 1878, **11**, 2070, 2073; von Braun and Weissbach, *loc. cit.*).

Synthetic methods available for the preparation of the required diamidine included the well-known Pinner synthesis (Pinner, *Ber.*, 1877, **10**, 1889; cf. Derby, *Amer. Chem. J.*, 1908, **39**, 437) through the imino-ether, and the recently-developed fusion methods using ammonium salts such as the benzenesulphonate (Oxley and Short, *J.*, 1946, 147) and thiocyanate (Partridge and Short, *J.*, 1947, 390).



(I.)



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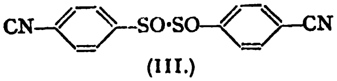


(III.)

$$3R\cdot SO_2H \longrightarrow R\cdot SO_2\cdot SR + R\cdot SO_2\cdot OH + H_2O \quad \ldots\ldots \quad (1)$$

Interaction of the disulphoxide (III) with ammonium thiocyanate at 180° (method *A*) gave a solid diamidine showing an intense colour in the Fuller reaction (Fuller, *Nature*, 1944, **154**, 773), and affording an 82·5% yield of a *dihydrochloride hemihydrate* (m. p. 316°) and from this an anhydrous *salt* (m. p. 310—311°) which gave analytical figures corresponding to di-*p*-amidinophenyl disulphide dihydrochloride. Further confirmation of the nature of the product was afforded by the preparation of the *dibenzenesulphonate*, *dipicrate*, and *dibenzoate dihydrate*.

This diamidine has been reported by Ashley *et al.* (*loc. cit.*) who obtained it by the Pinner synthesis from di-*p*-cyanophenyl disulphide and report m. p. >300° for the dihydrochloride dihydrate. In our hands the action of alcoholic hydrogen chloride on di-*p*-cyanophenyl disulphide (Bauer and Cymerman, *J.*, in the press) gave (method *D*) (*diphenyl disulphide*)-4 : 4'-*di*(*carboxyimino ethyl ether*) *dihydrochloride* in quantitative yield, and dry alcoholic ammonia converted this into the diamidine which gave a dibenzenesulphonate (53% yield) and dihydrochloride identical with those obtained from method *A*.

In order to examine the validity of the ammonium thiocyanate method in this case, interaction of di-*p*-cyanophenyl disulphide with this reagent was investigated (method *E*) and found to give the expected dibenzenesulphonate (35% yield), identical with that obtained from method *A*.

Attention was then turned to the alternative method of preparation using ammonium benzenesulphonate in the presence of ammonia gas (Oxley, Partridge, and Short, *J.*, 1948, 303). By this method the disulphoxide (III) at 180° (method *B*) afforded 51% of the dihydrochloride obtained in method *A*.

Finally, fusion of the disulphoxide (III) with ammonium benzenesulphonate alone at 250—255° (method *C*) yielded 81% of the dibenzenesulphonate identical with that obtained by method *A*. The aqueous mother-liquors afforded benzamidine-*p*-sulphonic acid (m. p. >360°) giving an intense amidine test (Fuller), completely soluble in sodium hydroxide solution (20%), and precipitated from this solution by hydrochloric acid (cf. Remsen and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 354). Disulphoxides are often regarded as reacting as the "thiolsulphonates" $R{\cdot}SO_2{\cdot}S{\cdot}R$ rather than as the symmetrical disulphoxides $R{\cdot}SO{\cdot}SO{\cdot}R$ (Gibson, Miller, and Smiles, *J.*, 1925, 1821; Gilman, Smith, and Parker, *J. Amer. Chem. Soc.*, 1925, **47**, 851; cf. however Fromm and Palma, *Ber.*, 1906, **39**, 3308; Hinsberg, *Ber.*, 1908, **41**, 2836, 4294; 1909, **42**, 1278). They are hydrolysed by alkali to a mixture of the disulphide and sulphinic acid (cf., *inter alia*, Pauly and Otto, *loc. cit.*; Bulmer and Mann, *J.*, 1945, 683); this has been variously postulated to proceed through the thiol (Otto and Rossing, *loc. cit.*), by hydrolytic fission (Zincke and Farr, *Annalen*, 1912, **391**, 58), through the sulphenic acid (Fromm, *loc. cit.*; Zincke, *Annalen*, 1914, **406**, 103), or by an oxidation–reduction mechanism (Zincke and Farr, *loc. cit.*), the overall reaction in every case being:

$$3R{\cdot}SO_2{\cdot}SR + 2H_2O \longrightarrow 4R{\cdot}SO_2H + RS{\cdot}SR \quad . \; . \; . \; . \; . \; . \quad (2)$$

The yields of di-*p*-amidinophenyl disulphide obtained by methods *A*, *B*, and *C*, however, all greatly exceed the theoretical figure calculated from reaction (2). It was shown by Halssig (*J. pr. Chem.*, 1897, **56**, 213) that the formation of disulphide and sulphonic acid from a sulphinic acid takes place, not only in an acidic environment, but also readily on warming the mixture in the presence of ammonia or by the action of heat on an ammonium sulphinate, according to reaction (1). Under the experimental conditions used, reactions (1) and (2) are thus consecutive and complementary, the net equation being (3):

$$5R{\cdot}SO_2{\cdot}SR + 2H_2O \longrightarrow 3RS{\cdot}SR + 4R{\cdot}SO_2{\cdot}OH \quad . \; . \; . \; . \; . \quad (3)$$

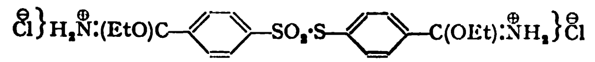
The expression (3) accounts satisfactorily for both the nature and the quantities of the two products obtained in methods *B* and *C*. The yields of diamidine obtained by method *A*, however, still exceed the theoretical amounts calculated from equation (3).

Disulphoxides are readily reduced to the corresponding disulphides by a variety of mild reducing agents (Hinsberg, *loc. cit.*; Smiles and Gibson, *loc. cit.*; Miller and Smiles, *J.*, 1925, 224) according to reaction (4); since ammonium thiocyanate, which at the reaction temperature (180°) exists as a mixture of thiourea, ammonia, hydrogen sulphide, and thiocyanic acid (Reynolds and Werner, *J.*, 1903, 1; Atkins and Werner, *J.*, 1912, 1172; Krall, *J.*, 1913, 1379), would be expected to possess reducing properties, direct reduction to the disulphide probably occurs during the reaction in method (*A*), the net reaction (5) being, in this case, a summation of (3) and (4). Calculation on this basis shows excellent agreement between the theoretical and experimental yields in method *A*.

$$2R{\cdot}SO_2{\cdot}SR + H_2 \longrightarrow 2R{\cdot}SO_2H + RS{\cdot}SR \quad . \; . \; . \; . \; . \; . \; . \quad (4)$$

$$4R{\cdot}SO_2{\cdot}SR + 3H_2 \longrightarrow 3RS{\cdot}SR + 2R{\cdot}SO_2{\cdot}OH + 2H_2O \quad . \; . \; . \; . \quad (5)$$

Since it had so far proved impossible to obtain the desired compound (I), the Pinner method was next applied to di-*p*-cyanophenyl disulphoxide (method *F*). Reaction with alcoholic hydrogen chloride readily afforded a theoretical yield of (*diphenyl disulphoxide*)-4 : 4'-*di*(*carboxyimino ethyl ether*) *dihydrochloride* (V) and from this the crystalline *hemihydrate* of the free base. With ethanolic ammonia the imino-ether hydrochloride gave quantitatively the diamidine dihydrochloride obtained by method *A*. The extremely ready conversion of disulphoxides in alkaline solution into the disulphides and sulphinic acids (equation 1) has been noted by many workers (cf. Kharasch, Potempa, and Wehrmeister, *Chem. Reviews*, 1946, **39**, 328; Otto and Rossing, *loc. cit.*), as has their contrasting stability in acid (Zincke and Eismayer, *Ber.*, 1918, **51**, 751). After treatment with dry ammonia in ethanol at room temperature the disulphoxide (III) was recovered quantitatively even after two weeks, but interaction in ethylene glycol at 180° afforded, as sole product, 56% (calculated from equation 3) of di-*p*-cyanophenyl disulphide. The ready conversion of the imino-ether hydrochloride (IV) into the disulphide is thus surprising and must be occasioned by the labilising effect of the cationic iminium group on the thiolsulphinate system in (IV), especially in view of the weak donor ability of sulphur compared with oxygen (Gordy and Stanford, *J. Amer. Chem. Soc.*, 1940, **62**, 498; Copley, Marvel, and Ginsberg, *ibid.*, 1939, **61**, 3161).


(IV.)

The melting point of (diphenyl disulphide)-4 : 4′(-dicarboxyimino ethyl ether) dihydrochloride (268—270°) lies very close to that of the corresponding diamide (278°), and it was found that the action of heat (180°) on the former gave an excellent yield of the latter. By this reaction (diphenyl disulphoxide)-4 : 4′-di(carboxyimino ethyl ether) dihydrochloride afforded quantitatively *di*-p-*carbamylphenyl disulphoxide*. This decomposition (reaction 6) by heat or storage is mentioned by Pinner (*loc. cit.*; cf. Shriner and Neumann, *Chem. Reviews*, 1944, **35**, 357), and Derby (*loc. cit.*) describes the isolation of benzamide from benzimino ethyl ether hydrochloride.

$$\mathrm{R{\cdot}C(OEt){:}\overset{\oplus}{N}H_2\}\overset{\ominus}{Cl}} \longrightarrow \mathrm{R{\cdot}CO{\cdot}NH_2 + EtCl} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Benzenesulphonates of imino-ethers appear not to have been described. Although *benzimino ethyl ether benzenesulphonate* was obtained in excellent yield as a crystalline solid, application of the same method to (IV) gave an uncrystallisable oil.

Ammonolysis of *N*-arylamidines to give the unsubstituted amidines according to equation (7) has been described by Pinner (*loc. cit.*; cf. Shriner and Neumann, *loc. cit.*) and by Oxley and Short (this vol., p. 449) and, since it occurs at a temperature lower than that required for the formation of an unsubstituted amidine from the corresponding cyanide, the possibility of obtaining (I) by this route, through the corresponding di-*N*-phenylamidino-compound was examined. Di-*p*-cyanophenyl disulphoxide and aniline benzenesulphonate (2 mols.) at 180° afforded a quantitative yield of a magnificent dark blue solid, which gave analytical figures for *di*-(p-N-*phenylamidinophenyl*) *disulphoxide dibenzenesulphonate* and showed solubilities in agreement with this structure. The material, softening at 100°, gave a blue solution in alcohol or acetone, from which it was reprecipitated unchanged by ether. Attempted preparation of the base by aqueous or alcoholic alkali was unsuccessful even after long refluxing. Ammonolysis of the blue material by gaseous ammonia, without a solvent or in ethylene glycol, at 180° for 6 hours gave only unchanged material.

$$\mathrm{R{\cdot}C({:}\overset{\oplus}{N}H_2){\cdot}NHR' + NH_3} \rightleftharpoons \mathrm{R{\cdot}C({:}\overset{\oplus}{N}H_2){\cdot}NH_2 + NH_2R'} \quad . \quad . \quad . \quad . \quad (7)$$

That the blue compound was not the corresponding disulphide derivative was shown by synthesis of the latter. Reaction of di-*p*-cyanophenyl disulphide and aniline benzenesulphonate at 220° gave *di*-(p-N-*phenylamidinophenyl*) *disulphide dibenzenesulphonate* as a white crystalline solid, m. p. 108°. Halssig (*loc. cit.*) reports that at 160—200° aniline toluene-*p*-sulphinate afforded a magnificent dark blue material which was physically and chemically similar to the blue product described above. Moreover, Halssig states that action of heat on the *p*-toluidine and *o*-toluidine salts of the same acid gave, respectively, a reddish-violet and a bluish-violet dye of very similar nature.

Heating a mixture of di-*p*-cyanophenyl disulphoxide and aniline did not give the blue dye, which was however obtained immediately by the addition of aniline benzenesulphonate to the melt. A mixture of diphenyl disulphoxide and aniline benzenesulphonate, when heated, also gave a deep-blue dye, and it was then found that a blue dye could also be produced from aniline benzenesulphonate alone by heating this to a higher temperature (250—300°) for a longer time. The nature of the blue dye was not further investigated.

In view of the ready conversion of disulphoxides into the corresponding disulphides and the resulting dependence on accurate analytical data, the ultra-violet absorption spectra of the compounds described above were determined (in alcohol) in order to investigate whether a generalisation capable of distinguishing between the two structures could be discovered.

Aromatic disulphides (p-R·C_6H_4·S)$_2$ (Table) have $\lambda_{\max.}$ at 2410 A. when R = H or Me (cf. also Fox and Pope, *J.*, 1913, 1263; Lyons, *Nature*, 1948, **162**, 1004; Koch, this vol., p. 394), and the introduction of an unsaturated bond into the group R causes a bathochromic and hyperchromic displacement of +300—400 A. (Fig. 1).

Fig. 1.

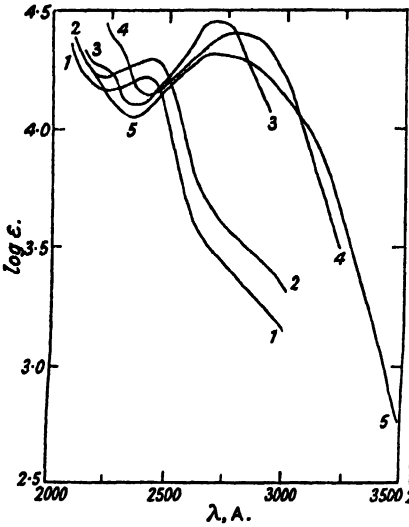


Fig. 2.

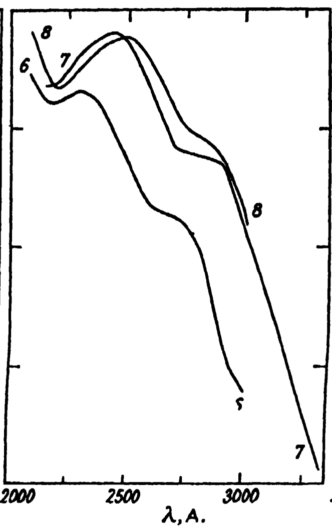
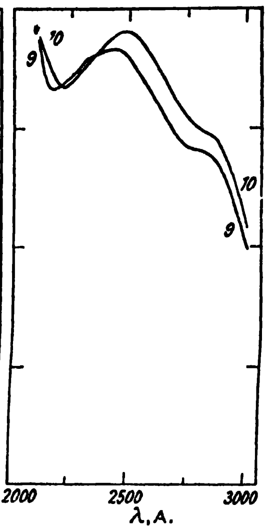


Fig. 3.



1. *Diphenyl disulphide*.—2. *Di*-p-*tolyl disulphide*.—3. *Di*-p-*cyanophenyl disulphide*.—4. *Di*-p-*amidinophenyl disulphide dibenzenesulphonate*.—5. (*Diphenyl disulphide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *dihydrochloride*.—6. *Diphenyl disulphoxide*.—7. *Di*-p-*cyanophenyl disulphoxide*.—8. (*Diphenyl disulphoxide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *hydrochloride*.—9. *Di*-p-*carbamylphenyl disulphoxide*.—10. *Diphenyl disulphoxide di*(*imino ethyl ether*).

The corresponding disulphoxides p-R·C_6H_4·SO_2·S·C_6H_4·R-p (Table), in which one sulphur atom is devoid of unshared electrons, have $\lambda_{\max.}$ at 2300 A. when R = H, while the bathochromic and hyperchromic displacement caused by the introduction of an unsaturated centre into the group R of the disulphoxides is much smaller (+150 to 200 A.) than it is for the corresponding disulphides. The disulphoxides examined show a characteristic marked inflexion at 2720—2900 A. (Figs. 2 and 3).

Absorption spectra of disulphides, (p-R·C_6H_4·S)$_2$, *and disulphoxides*, p-R·C_6H_4·SO_2·S·C_6H_4·R-p.

	Disulphide.		Disulphoxide.	
R =	$\lambda_{\max.}$, A.	log $\varepsilon_{\max.}$.	$\lambda_{\max.}$, A.	log $\varepsilon_{\max.}$.
H	2410	4·22	2300—2310 2720 *	4·15 3·60
Me	2420	4·29	—	—
NH_2,HCl	2540—2560 2900	4·21 3·91	—	—
CN	2670—2730	4·41	2430—2440 2910 *	4·40 3·85
$C{<}^{OEt}_{NH}$	—	—	2490—2500 2830 *	4·40 3·99
$C{<}^{OEt}_{NH_2Cl}$	2710—2750	4·31	2460—2480 2830 *	4·39 3·96
$C{<}^{NH_2}_{NH_2Cl}$	2800—2840	4·38	—	—
$C{<}^{NH_2}_{NH_2X}$ †	2800—2850	4·39	—	—
CO·NH_2	—	—	2400—2440 2830 *	4·34 3·88

* Inflexion. † X = C_6H_5·SO_3.

Examination of the ultra-violet absorption spectra thus not only affords valuable confirmatory evidence of the structure of (IV) but also makes it possible to distinguish readily between aromatic disulphides and disulphoxides.

EXPERIMENTAL.

*Di-*p*-cyanophenyl Disulphoxide.*—A solution of sodium *p*-cyanobenzenesulphinate (18·9 g., 0·1 mol.) in water (135 c.c.) was cooled to 0° and acidified strongly with concentrated hydrochloric acid (250 c.c.). The solution was set aside at 0° for 2 days, saturated with salt, and extracted with chloroform. Removal of solvent from the washed and dried (Na_2SO_4) chloroform extracts and crystallisation of the residue from alcohol gave white needles (7 g., 70%) of di-*p*-cyanophenyl disulphoxide, m. p. 158—159° (Cymerman, Koebner, and Short, *loc. cit.*, give m. p. 158—159°).

The original aqueous mother-liquors after extraction with chloroform were evaporated to half-bulk *in vacuo* and filtered, and the filtrate was treated with a solution of *p*-toluidine (7 g.) in hot dilute hydrochloric acid (5N.; 100 c.c.). Cooling to 0° gave white plates (4 g., 45%) of p-*toluidine* p-*cyanobenzenesulphonate* (Found: N, 9·55. $C_{14}H_{14}O_3N_2S$ requires N, 9·65%), m. p. 241°, undepressed on admixture with an authentic specimen (m. p. 241°) prepared from *p*-cyanobenzenesulphonyl chloride.

*Di-*p*-amidinophenyl Disulphide.*—*Method* A. (*a*) A mixture of di-*p*-cyanophenyl disulphoxide (4·5 g.) and ammonium thiocyanate (11 g., 10 mols.) was heated at 180° (bath temperature) for 3 hours with stirring. The cooled melt was then extracted with boiling water (300 c.c.) and filtered, and the filtrate basified at 0° (ice) with sodium hydroxide solution (10N.). The precipitated diamidine was collected on a funnel, washed with ice-water, and dissolved in the minimum amount of boiling hydrochloric acid (5N.). Cooling afforded white needles of *di-*p*-amidinophenyl disulphide dihydrochloride hemihydrate* (3·5 g., 82·5%), m. p. 316° (Found: N, 14·6; H_2O, 2·1. $C_{14}H_{16}N_4Cl_2S_2,\frac{1}{2}H_2O$ requires N, 14·6; H_2O, 2·35%). Drying at 120° gave the anhydrous *salt* (Found: C, 45·1; H, 4·35; N, 14·8, 14·75. $C_{14}H_{16}N_4Cl_2S_2$ requires C, 44·8; H, 4·3; N, 14·9%), m. p. 310—311°.

(*b*) The base precipitated from a fusion identical with that of (*a*) was dissolved in the minimum of hot aqueous benzenesulphonic acid. On cooling, *di-*p*-amidinophenyl disulphide dibenzenesulphonate* separated (6·75 g., 97%) as white needles, m. p. 253—254° (Found: C, 50·3; H, 4·2; N, 8·95. $C_{26}H_{26}O_6N_4S_4$ requires C, 50·5; H, 4·2; N, 9·05%).

(*c*) Equivalent quantities of the diamidine dihydrochloride and sodium picrate in the minimum of hot water were mixed and the quantitatively-formed yellow precipitate was recrystallised from aqueous 2-ethoxyethanol, giving the *dipicrate* as yellow needles, m. p. 257° (decomp). (Found: N, 18·35. $C_{26}H_{20}O_{14}N_{10}S_2$ requires N, 18·4%).

(*d*) Addition of excess of sodium benzoate solution to a solution of the diamidine dihydrochloride and recrystallisation of the white precipitate from methanol–ether afforded white crystals of the *dibenzoate dihydrate*, m. p. 250° (decomp.) (Found: C, 58·05, 58·1; H, 4·85, 5·05; N, 9·65, 9·5. $C_{28}H_{26}O_4N_4S_2,2H_2O$ requires C, 57·75; H, 5·15; N, 9·6%).

Method B. (*a*) A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and ammonium benzenesulphonate (7 g., 2 mols.) was stirred at 180° (bath) in an atmosphere of ammonia for 7 hours, the mixture becoming mobile after 2—3 hours. It was extracted with boiling water (400 c.c.), the filtrate basified at 0° (ice) with sodium hydroxide solution (10N.) and the base washed with ice-water on the filter. Dissolved in the minimum of hot dilute hydrochloric acid (5N.), it gave on cooling white needles of di-*p*-amidinophenyl disulphide dihydrochloride (2·3 g., 51%), m. p. 310—311° (decomp.), undepressed on admixture with the substance (m. p. 310—311°) from method *A* (Found: C, 44·8, 44·5, 45·1; H, 4·2, 4·05, 4·5; N, 14·35, 14·35%).

(*b*) An identical fusion, followed by dissolution of the base obtained in benzenesulphonic acid afforded the dibenzenesulphonate, m. p. 253—255° (4·8 g., 65%), as white needles (Found: C, 49·7; H, 4·7; N, 8·65%). It did not depress the m. p. of a sample (m. p. 253—254°) from method *A*.

(*c*) The dipicrate was obtained as very small yellow crystals (from 2-ethoxyethanol), m. p. 259° (decomp.) (Found: N, 17·75%), undepressed on admixture with the substance (m. p. 257°) from method *A*.

(*d*) The dibenzoate dihydrate was obtained as white crystals, m. p. 249° (decomp.) (Found: C, 58·1; H, 4·75; N, 9·33%). A mixed m. p. with the material (m. p. 250°) from method *A* was undepressed.

Method C. A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and ammonium benzenesulphonate (14 g., 4 mols.) was heated at 250—255° for 2 hours. The reaction mixture was extracted with boiling water, and the filtrate on cooling deposited white needles (6 g., 81%) of the dibenzenesulphonate, m. p. 250—254° (Found: C, 50·15; H, 4·4; N, 8·95%), undepressed on admixture with a sample (m. p. 253—254°) from method *A*. The aqueous mother-liquors on evaporation to dryness *in vacuo* left a solid residue (12 g.) from which ammonium benzenesulphonate was removed by extraction with cold water, leaving a white solid (2 g., 62·5%) crystallising from hot water in needles, m. p. >360°, of benzamidine-*p*-sulphonic acid (Found: N, 13·85. Calc. for $C_7H_8O_3N_2S$: N, 14·0%). Remsen and Muckenfuss (*Amer. Chem. J.*, 1896, **18**, 353) give m. p. >360°.

Method D. A solution of di-*p*-cyanophenyl disulphide (0·9 g.) in dry chloroform (20 c.c.) and dry alcohol (10 c.c.) was saturated with hydrogen chloride at 0° and set aside at room temperature for 8 days. Addition of dry ether gave (*diphenyl disulphide*)-4 : 4'-*di*(*carboxyimino ethyl ether*) *dihydrochloride* (1·4 g., 96%) as a white microcrystalline solid, m. p. (sealed tube) 268—270° (decomp.) after foaming at 120° (Found: N, 6·5. $C_{18}H_{22}O_2N_2Cl_2S_2$ requires N, 6·5%).

The dihydrochloride (1 g.) was suspended in dry alcohol (20 c.c.) saturated with ammonia at 0°, and set aside for 10 days. The alcoholic solution was poured into dry ether, the precipitate dissolved in dilute hydrochloric acid, and converted, *via* the base, into the diamidine dibenzenesulphonate (0·75 g., 53%), m. p. 252—255° (Found: N, 8·95%), which did not depress the m. p. of a sample (m. p. 253—254°) prepared by method *A*. This was converted, *via* the base, into the dihydrochloride, m. p. 310—311°

(Ashley, Barber, Ewins, Newbery, and Self, *loc. cit.*, give m. p. >300°), which did not depress the m. p. of the material (m. p. 310—311°) obtained by method *A*.

Method E. A mixture of di-*p*-cyanophenyl disulphide (2 g.) and ammonium thiocyanate (6 g.) was heated at 180° (bath) for 3 hours with stirring. Working-up as described above (method *A*) afforded white needles (1·6 g., 35%) of the dibenzenesulphonate, m. p. 253—255°, undepressed on admixture with a sample (m. p. 253—254°) prepared by method *A* (Found : N, 8·6, 8·5%).

The picrate crystallised from acetone–light petroleum (b. p. 40—60°) in yellow needles, m. p. 255° (decomp.) (Found : N, 18·1%), which showed no depression when mixed with the substance (m. p. 257°) from method *A*.

Method F. (*a*) A solution of di-*p*-cyanophenyl disulphoxide (6 g.) in chloroform (70 c.c.) and absolute alcohol (40 c.c.) was treated with dry hydrogen chloride at 0°, set aside at room temperature for 5 days, and then shaken for 6 hours. Addition of dry ether afforded (*diphenyl disulphoxide*) 4 : 4′-*di*(*imino diethyl ether*) *dihydrochloride* (9·2 g., 100%) as a white solid, m. p. (sealed tube) 225—230° (decomp.) after foaming at 120°, and forming a meniscus at 275—280° (Found: C, 45·9; H, 4·9; N, 6·25. $C_{18}H_{22}O_4N_2Cl_2S_2$ requires C, 46·5; H, 4·7; N, 6·0%).

(*b*) A mixture of this dihydrochloride (0·5 g.), anhydrous potassium carbonate (0·5 g.), and chloroform (50 c.c.) was shaken with water (25 c.c.), and the chloroform layer separated. The aqueous phase was extracted with chloroform, and the combined extracts dried (Na_2SO_4). Removal of solvent to small bulk and addition of light petroleum (b. p. 40—60°) afforded white cubes of (*diphenyl disulphoxide*)-4 : 4′-*di*(*carboxyimino ethyl ether*) *hemihydrate*, m. p. 220° (decomp.) (Found : C, 53·9; H, 5·6; N, 6·75, 6·55. $C_{18}H_{20}O_4N_2S_2,\frac{1}{2}H_2O$ requires C, 53·9; H, 5·3; N, 7·0%).

(*c*) A solution of the dihydrochloride obtained in (*a*) above (4·5 g.) in absolute alcohol (50 c.c.) saturated with ammonia at 0° was allowed to stand for 6 days. Addition of ether gave the crude diamidine dihydrochloride (4·0 g., 100%) which after purification *via* the base had m. p. 310—311°, undepressed on admixture with the compound (m. p. 310—311°) from method *A*. This was converted into the dibenzenesulphonate, m. p. 253—254° (Found : C, 50·1; H, 4·6; N, 8·95%) which showed no depression with the compound (m. p. 253—254°) from method *A*.

Di-p-*carbamylphenyl Disulphide*.—A small quantity of diphenyl disulphide 4 : 4′-di-imino diethyl ether dihydrochloride was heated at 180° (bath) for 1 hour. The residue, crystallised from acetic acid, gave white needles of di-*p*-carbamylphenyl disulphide, m. p. 276—277°. A mixed m. p. with an authentic specimen (McClelland and Warren, *J.*, 1930, 1102; m. p. 278°) gave no depression.

Di-p-*carbamylphenyl Disulphoxide*.—Heated at 180° (bath) for 1 hour, the disulphoxide di-iminoether dihydrochloride (0·5 g.) afforded 0·48 g. (100%) of *di*-p-*carbamylphenyl disulphoxide* as a white microcrystalline solid, m. p. 225—230° (decomp.), forming a meniscus at 275—280° (Found: N, 8·35. $C_{14}H_{12}O_4N_2S_2$ requires N, 8·35%).

Action of Ammonia on Di-p-*cyanophenyl Disulphoxide*.—A solution of di-*p*-cyanophenyl disulphoxide (0·5 g.) in ethylene glycol (10 c.c.) was kept at 180° for 2 hours in an atmosphere of ammonia. The solution was cooled, poured into water, and extracted with chloroform. Removal of solvent from the dried chloroform extracts afforded a residue (0·15 g.) which when purified by sublimation (0·01 mm.) and crystallisation from chloroform–light petroleum (b. p. 40—60°) had m. p. 165—168°, undepressed on admixture with di-*p*-cyanophenyl disulphide (m. p. 172—173°). A mixture with the starting material (m. p. 157—158°) gave a 30° depression in m. p.

Di-(p-N-*phenylamidinophenyl*) *Disulphoxide Dibenzenesulphonate*.—A mixture of di-*p*-cyanophenyl disulphoxide (6 g.) and aniline benzenesulphonate (10 g., 2 mols.) was heated at 180° (bath) for 2 hours, the mixture becoming mobile after 0·5 hour and then viscous after 1·4 hours. The cooled reaction mixture, recrystallised from alcohol–ether, gave a deep-blue *salt* (16 g., 100%), softening at 100° (Found : N, 7·0. $C_{38}H_{34}O_8N_4S_4$ requires N, 7·0%). It was soluble in methanol or acetone, moderately soluble in alcohol, sparingly soluble in *iso*propanol or water, and insoluble in ether.

Di-(p-N-*phenylamidinophenyl*) *Disulphide Dibenzenesulphonate*.—A mixture of di-*p*-cyanophenyl disulphide (0·1 g.) and aniline benzenesulphonate (0·38 g.) was heated at 220° (bath) for 2 hours. Extraction with boiling water afforded, on cooling, white prisms of the *dibenzenesulphonate*, m. p. 108° (Found : N, 6·85, 6·85. $C_{38}H_{34}O_6N_4S_4$ requires N, 7·25%).

Benzimino Ethyl Ether Benzenesulphonate.—Equivalent quantities of the benzimino-ether hydrochloride and potassium carbonate in the minimum amount of water were mixed and the free base was at once extracted with ether. The dried (Na_2SO_4) ethereal solution was added to a solution of benzenesulphonic acid in methanol. Cooling gave colourless needles, m. p. 137°, of *benzimino ethyl ether benzenesulphonate* (Found : N, 4·6. $C_{15}H_{17}O_4NS$ requires N, 4·55%).

This work was carried out under the auspices of the National Health and Medical Research Council, to whom thanks are due for financial assistance. The authors also thank Miss J. Fildes for microanalyses and Dr. W. F. Short for kindly affording facilities for a number of microanalyses.

ORGANIC CHEMISTRY DEPARTMENT, UNIVERSITY OF SYDNEY. [*Received, August* 31*st*, 1949.]

24. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part I. The Synthesis of a Geometrical Isomer of Herculin.*

By R. A. RAPHAEL and FRANZ SONDHEIMER.*

Attempts to synthesise the insecticide herculin (I; configuration about the double bonds unknown) are described. The diacetylenic analogue (VI) and the *cis*-ethylenic-acetylenic analogue (XV) have been prepared by the methods indicated in the scheme on p. 116. Partial hydrogenation of these compounds gave the *iso*butylamide of undeca-1(*cis*) : 7(*cis*)-diene-1-carboxylic acid (*cis-cis* herculin) (I); this was not identical with the natural insecticide.

A PUNGENT *N-iso*butyl unsaturated acid amide has been isolated from the bark of the southern prickly ash, *Zanthoxylum clavaherculis* L., by Jacobson (*J. Amer. Chem. Soc.*, 1948, **70**, 4234). The substance, which was shown to have the structure (I) (*N-iso*butylundeca-1 : 7-diene-1-carboxyamide), has approximately the same order of paralysing action and toxicity to house flies as the pyrethrins, and is also toxic to several other species of insects. When the synthesis of a compound of this structure is considered, it becomes apparent that any one of four configurations is possible according to the geometrical isomerism about the double bonds (*trans-trans*, *trans-cis*, *cis-trans*, and *cis-cis*). No speculation about the configuration of the natural compound was made by Jacobson.

We have synthesised by two routes a compound of structure (I), possessing the *cis*-configuration about both double bonds; this, however, was not identical with natural herculin, and the latter must therefore have one of the three remaining configurations.

When octa-1 : 7-diyne (II) (prepared from tetramethylene dibromide and sodium acetylide as described by Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619) was treated first with 1·1 moles of sodamide in liquid ammonia, and then with propyl iodide, the required monoalkylation product *undeca*-1 : 7-*diyne* (III) was obtained in 86% yield (allowing for the recovered starting material). This type of differential condensation of a diacetylene has been found to be of general applicability, and it has been employed in other syntheses (Sondheimer, forthcoming publication; Leese and Raphael, forthcoming publication). The Grignard complex of (III) was carbonated with solid carbon dioxide at atmospheric pressure to give *undeca*-1 : 7-*diyne*-1-*carboxylic acid* (IV) (S-*benzylthiuronium* salt) in 65% yield, the structure of which was confirmed by hydrogenation to lauric acid. Heating (IV) under reflux with oxalyl chloride (cf. Adams and Ulich, *J. Amer. Chem. Soc.*, 1920, **42**, 599) produced the acid chloride (V) which on treatment with excess of *iso*butylamine furnished the crystalline diacetylenic N-iso*butyl-amide* (VI) in excellent yield. When this absorbed two moles of hydrogen in the presence of a palladium–calcium carbonate catalyst, N-iso*butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*herculin*) (I) was obtained as a homogeneous liquid.

The formulation of this compound, and others described below, as the *cis-cis*-isomer, is based on many recorded observations regarding the catalytic hydrogenation of triple bonds (*inter al.*, Bourguel, *Bull. Soc. chim.*, 1929, **45**, [4], 1067; Stoll and Rouvé, *Helv. Chim. Acta*, 1938, **21**, 1542; *idem*, *Ber.*, 1940, **73**, 1358; Campbell *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 216, 2683; *Chem. Reviews*, 1942, **31**, 90; Lauer and Gensler, *J. Amer. Chem. Soc.*, 1945, **67**, 1171; Ahmad, Bumpus, and Strong, *ibid.*, 1948, **70**, 3391). However, infra-red absorption has indicated that this type of hydrogenation (employing a palladium–calcium carbonate catalyst at room temperature) may also give rise to a small proportion of the *trans*-isomer (Sondheimer, forthcoming publication); for convenience this fact is neglected in the nomenclature of the hydrogenation compounds described in this paper.

Alternatively, the acid (IV) was partially hydrogenated to *undeca*-1(cis) : 7(cis)-*diene*-1-*carboxylic acid* (VII) (S-*benzylthiuronium* salt). The structure of this acid was confirmed by its light-absorption properties, the intensity of absorption at 2160 A. being double that of the unchanged acetylenic acid (IV) (cf. Braude, *Ann. Reports*, 1945, **42**, 105; Haynes and Jones, *J.*, 1946, 503). Heating this acid under reflux with oxalyl chloride gave the corresponding acid chloride, which, undistilled, reacted with *iso*butylamine to product an excellent yield of (I), identical with that obtained above.

The second route to *cis-cis*-herculin (I) employs the differential reaction of a mixed dihalide with a sodium acetylide (cf. Henne and Greenlee, *J. Amer. Chem. Soc.*, 1945, **67**, 484; Ahmad, Strong, *et al.*, *ibid.*, 1948, **70**, 1699, 3391; Newman and Wotiz, *ibid.*, 1949, **71**, 1292).

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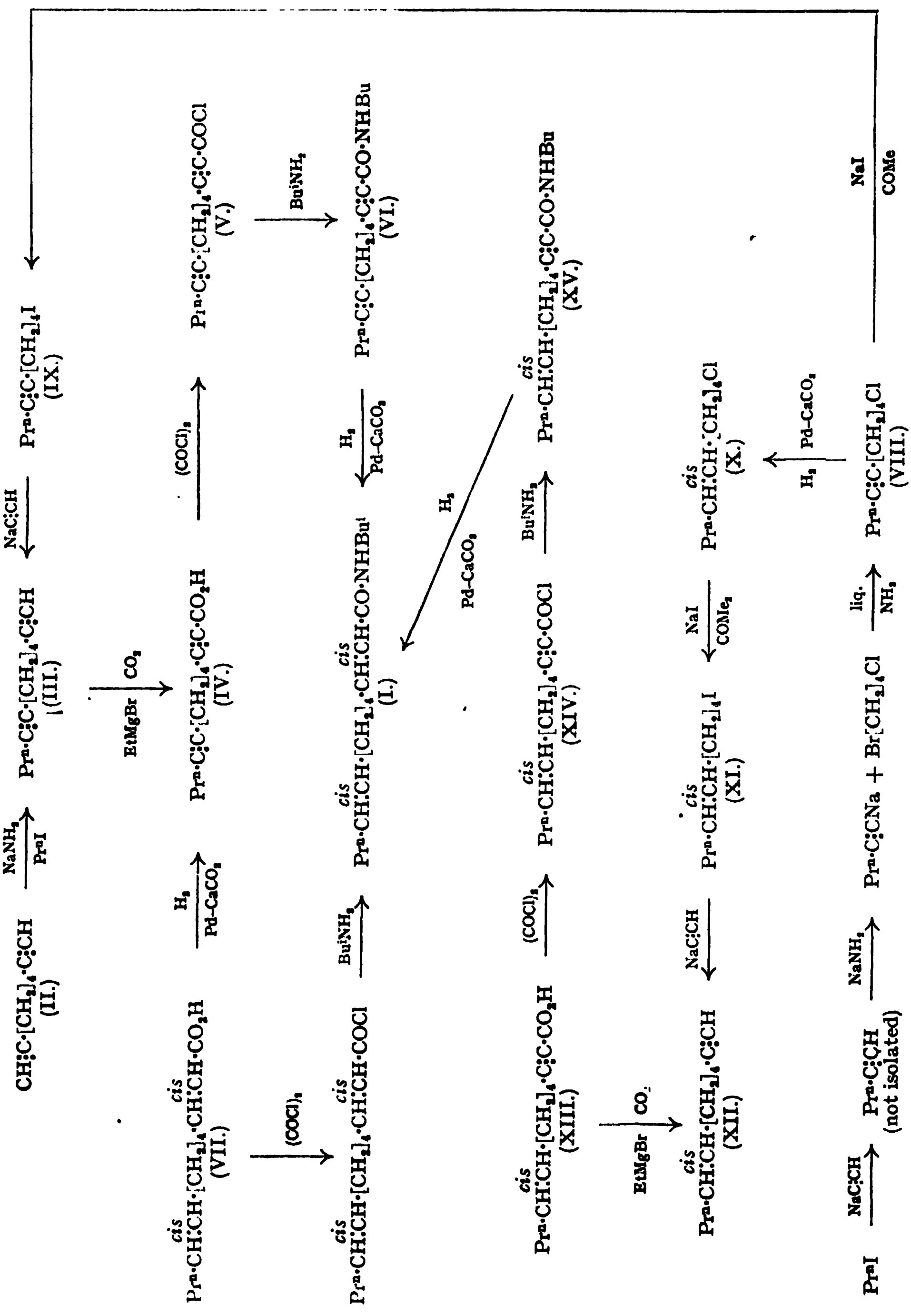
* This work was started independently by the two authors; when this was realised, it was decided to publish the results jointly.


CH:C·[CH2]4·C:CH
(II.)
NaNH2
PrnI
Prn·C:C·[CH2]4·C:CH
(III.)
NaC:CH
Prn·C:C·[CH2]4I
(IX.)
EtMgBr
CO2
Prn·C:C·[CH2]4·C:C·CO2H
(IV.)
(COCl)2
Prn·C:C·[CH2]4·C:C·COCl
(V.)
BuiNH2
Prn·C:C·[CH2]4·C:C·CO·NHBui
(VI.)
H2
Pd-CaCO3
cis cis
Prn·CH:CH·[CH2]4·CH:CH·CO2H
(VII.)
(COCl)2
cis cis
Prn·CH:CH·[CH2]4·CH:CH·COCl
BuiNH2
cis cis
Prn·CH:CH·[CH2]4·CH:CH·CO·NHBui
(I.)
H2
Pd-CaCO3
cis
Prn·CH:CH·[CH2]4·C:C·CO2H
(XIII.)
(COCl)2
cis
Prn·CH:CH·[CH2]4·C:C·COCl
(XIV.)
BuiNH2
cis
Prn·CH:CH·[CH2]4·C:C·CO·NHBui
(XV.)
EtMgBr
CO2
cis
Prn·CH:CH·[CH2]4·C:CH
(XII.)
NaC:CH
cis
Prn·CH:CH·[CH2]4I
(XI.)
NaI
COMe2
cis
Prn·CH:CH·[CH2]4Cl
(X.)
H2
Pd-CaCO3
Prn·C:C·[CH2]4Cl
(VIII.)
NaI
COMe2
PrnI
NaC:CH
Prn·C:CH
(not isolated)
NaNH2
Prn·C:CNa + Br[CH2]4Cl
liq.
NH3

Condensation of propyl iodide with sodium acetylide (this must not be made from sodamide; see Experimental) in liquid ammonia gave pent-1-yne, which, because of its volatility, was not isolated, but converted into its sodium salt by addition of 1 mole of sodamide. Reaction with 1-chloro-4-bromobutane (prepared from tetrahydrofuran as described by Newman and Wotiz, *loc. cit.*) gave 1-*chloronon-5-yne* (VIII) in 64% yield. Refluxing the chloro-compound with sodium iodide in acetone gave the iodo-compound (IX) which was condensed without purification with sodium acetylide in liquid ammonia. The undeca-1 : 7-diyne (III) thus obtained in 44% yield had identical physical properties with that obtained above.

Partial hydrogenation of the acetylenic chloride (VIII) in the presence of a palladium–calcium carbonate catalyst, or better Raney nickel, gave 1-*chloronon*-5(cis)-*ene* (X), which when heated under reflux with sodium iodide in acetone yielded the iodide (XI). The crude iodide was condensed with sodium acetylide in liquid ammonia whereby *undec*-7(cis)-*en*-1-*yne* (XII) was obtained in 62% yield [based on (X)]. Carbonation of the Grignard complex of (XII) at atmospheric pressure gave *undec*-7(cis)-*en*-1-*yne*-1-*carboxylic acid* (XIII) in 57% yield. The acid chloride (XIV), prepared by refluxing the acid with oxalyl chloride, was condensed with excess of *iso*butylamine and N-iso*butylundec*-7(cis)-*en*-1-*yne*-1-*carboxyamide* (XV) was formed. Partial hydrogenation in the presence of a palladium–calcium carbonate catalyst then gave *cis*-*cis*-herculin (I), having physical properties identical with those of (I), prepared as above.

The *cis*-*cis*-analogue (I), obtained by these routes, was a colourless liquid, which could not be induced to crystallise, whereas natural herculin is a crystalline solid, m. p. 59—60°. Moreover it was quite stable at room temperature, whereas natural herculin (Jacobson, *loc. cit.*) has been reported to be unstable under these conditions. Again it shows none of the physiological properties (burning taste, etc.) described by the American author.

The structure of (I) was rigidly confirmed by complete hydrogenation to the crystalline *N*-*iso*butyl-lauramide, and by potassium permanganate oxidation, whereby the three fragments (butyric, adipic, and *N*-*iso*butyloxamic acids) were isolated in yields very similar to those obtained by Jacobson (*loc. cit.*) for the natural herculin.

The three herculin analogues, *cis*-*cis*-herculin (I), 1 : 2-dehydro-*cis*-herculin (XV), and 1 : 2 : 7 : 8-tetradehydroherculin (VI), are being tested by Dr. R. A. E. Galley of the Agricultural Research Council for insecticidal properties, and the results will be recorded later.

Attempts to convert both the *cis*-*cis*-acid (VII) and the *cis*-*cis*-*N*-*iso*butyl-amide (I) into the *trans*-*trans*-compounds by various methods have so far been unsuccessful. Thus even when the acid (VII) was heated with selenium at 200° for 10 minutes (cf. Ahmad, Bumpus, and Strong, *J. Amer. Chem. Soc.*, 1948, **70**, 3391), it was recovered unchanged. It is known however that the partial reduction of an acetylene with sodium in liquid ammonia leads to the *trans*-ethylenic compound (Campbell and Eby, *J. Amer. Chem. Soc.*, 1941, **63**, 216, 2683; Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 90; Sondheimer, forthcoming publication). Application of this method to the analogues (VI) and (XV) should furnish the 1(*trars*) : 7(*trans*)- and 1(*trans*) : 7(*cis*)-herculins. It is now considered that the latter isomer will most probably be identical with the natural compound (cf. the short discussion presented in the following paper regarding the stereochemical configuration of the closely related insecticide, pellitorine), and further work on these compounds is now in progress in these laboratories. Moreover the methods described in this paper are being used for the synthesis of the various possible stereoisomers of other related insecticides, and the preparation of a geometrical isomer of the insecticide pellitorine is described in the following communication.

EXPERIMENTAL.

(Light-absorption data were determined in ethanol.)

Undeca-1 : 7-*diyne* (III).—To a suspension of sodamide in liquid ammonia (150 c.c.) [from sodium (5·0 g.), the ferric nitrate catalyst described by Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used to catalyse the transformation] octa-1 : 7-diyne (21·2 g.) in dry ether (25 c.c.) was added during 10 minutes with stirring and cooling (alcohol–carbon dioxide). The reaction mixture was stirred for 2 hours, and propyl iodide (41 g.) in ether (30 c.c.) was gradually added. Stirring was continued for another 6 hours, the temperature being kept at *ca.* —40°. The solvent was evaporated on the steam-bath, water and ether were added, and the ether layer after being washed with water, dilute sulphuric acid, and sodium hydrogen carbonate solution, was dried and evaporated. Distillation of the residue through a short Vigreux column gave unchanged octadiyne (9·2 g.) and *undeca*-1 : 7-*diyne* (14·4 g., 86% yield, 49% conversion) as a mobile pleasant-smelling liquid, b. p. 97—99°/20 mm., n_D^{20} 1·4576 (Found: C, 88·75; H, 10·9. $C_{11}H_{16}$ requires C, 89·1; H, 10·9%). In addition, a product (2·1 g.) was obtained, b. p. 135—140°/18 mm., n_D^{20} 1·4650, believed to be the dialkylation product, tetradeca-4 : 10-diyne; this was not further investigated.

When propyl bromide was substituted for the iodide in the above experiment, the yield of undecadiyne was considerably reduced.

Undeca-1 : 7-*diyne*-1-*carboxylic Acid* (IV).—Undeca-1 : 7-diyne (7·4 g.) in dry ether (20 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·6 g.) in ether (120 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 90 minutes, and then cooled in ice. It was poured on to a large excess of solid carbon dioxide in a conical flask, and the flask was shaken occasionally. After *ca.* 1 hour, when most of the solid had disappeared, more solid carbon dioxide was added, and the mixture was set aside overnight. The solid complex was decomposed with dilute sulphuric acid, and the ethereal layer was washed with water and sodium hydrogen carbonate solution. The latter extract was washed with ether, acidified, and again shaken with ether. This last ether extract was dried, evaporated, and the residue distilled. *Undeca*-1 : 7-*diyne*-1-*carboxylic acid* (6·2 g., 65%) was obtained as a colourless liquid, b. p. 134—135°/10^{-2} mm., n_D^{16} 1·4882 (Found : C, 75·3; H, 8·55. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). Light absorption : $\varepsilon = 6{,}700$ (λ, 2160 A.). The S-*benzylthiuronium* salt crystallised from a large volume of ethyl acetate in plates, m. p. 174° (Found: C, 67·25; H, 7·45; N, 7·95. $C_{20}H_{26}O_2N_2S$ requires C, 67·0; H, 7·3; N, 7·8%).

The acid (0·55 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (274 c.c. of gas were absorbed at 16°/780 mm., equivalent to 4·05 ⊨). The residue (0·56 g.), after removal of the catalyst and solvent, completely solidified, and then had m. p. 43° undepressed on admixture with an authentic sample of lauric acid.

Undeca-1 : 7-*diyne*-1-*carboxyl Chloride.* (V).—The diacetylenic acid (3·0 g.) and oxalyl chloride (7·5 g.) were heated under reflux for 40 minutes (gas evolution ceased after *ca.* 25 minutes). The excess of oxalyl chloride was removed at the water-pump, the temperature being kept below 60°. The residue was rapidly distilled to give the acid chloride (2·8 g.) as a mobile pungent liquid, b. p. 97—99°/10^{-2} mm., n_D^{20} 1·4903, which hydrolysed too rapidly in air to permit of accurate analysis.

In another experiment, in which the excess of oxalyl chloride was removed at too high a temperature, considerable polymerisation occurred, and only a very poor yield of the required acid chloride was obtained.

N-iso*Butylundeca*-1 : 7-*diyne*-1-*carboxyamide* (VI).—A solution of *iso*butylamine (4·5 g.) in dry ether (10 c.c.) was added dropwise during 5 minutes to the diacetylenic acid chloride (V) (2·6 g.) in ether (10 c.c.), with ice cooling and continuous shaking. After 1 hour at room temperature, the reaction mixture was diluted with more ether and washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated to give the diacetylenic N-iso*butyl-amide* (2·95 g.) as a colourless liquid, which completely solidified on cooling and then had m. p. 45—47°. One crystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 47—48°, not raised by further crystallisation (Found : C, 77·35; H, 10·35; N, 5·65. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·2; N, 5·65%).

N-iso*Butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*Herculin*) (I) *from* (VI).—The diacetylenic *N-iso*butyl-amide (VI) (1·14 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·14 g.; 2% Pd) until 2 moles of hydrogen (222 c.c. at 18°/768 mm.) had been absorbed. The residue, after removal of the catalyst and solvent, was distilled to give cis-cis-*herculin* (0·91 g.) as a colourless liquid, b. p. 140—142°/10^{-3} mm., n_D^{17} 1·4838 (Found : C, 76·25; H, 11·7; N, 5·65. $C_{16}H_{29}ON$ requires C, 76·45; H, 11·65; N, 5·55%).

Undeca-1(cis) : 7(cis)-*diene*-1-*carboxylic Acid* (VII).—The diacetylenic acid (IV) (4·68 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·3 g.; 2% Pd) until 2 moles of hydrogen (1174 c.c. at 19°/771 mm.) had been absorbed (no reaction of the calcium carbonate substrate with the acid was detectable). The catalyst was filtered off, the solvent evaporated, and the residue distilled. This gave the diethylenic *acid* (4·3 g.) as a colourless liquid, b. p. 108—109°/10^{-4} mm., n_D^{20} 1·4740—1·4742 (Found : C, 73·9; H, 10·55. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·3%). Light absorption : $\varepsilon = 13{,}700$ (λ, 2160 A.). The S-*benzylthiuronium* salt crystallised from ethyl acetate in plates, m. p. 129—130° (Found : N, 7·85. $C_{20}H_{30}O_2N_2S$ requires N, 7·75%).

N-iso*Butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*Herculin*) (I) *from* (VII).—The diethylenic acid (1·4 g.) (VII) and oxalyl chloride (3·6 g.) were heated under reflux for 1 hour. The excess of oxalyl chloride was removed at the water-pump, and dry benzene was added to the residue, which was again concentrated at the water-pump to give the crude acid chloride (1·65 g.) as a yellow pungent liquid, n_D^{21} 1·4800.

A solution of *iso*butylamine (2·7 g.) in dry ether (10 c.c.) was added dropwise during 5 minutes to the crude acid chloride (1·63 g.) in ether (10 c.c.), with ice-cooling and continuous shaking. After 20 minutes, the product was isolated as described above, and distillation gave *cis-cis*-herculin (1·6 g.), b. p. 145—146°/10^{-3} mm., n_D^{21} 1·4824—1·4827.

1-*Chlorononon*-5-*yne* (VIII).—Sodium (5·5 g.), in small pieces, was added to liquid ammonia (300 c.c.) through which acetylene was bubbled, with stirring and cooling (alcohol–carbon dioxide), at such a rate that the blue colour just disappeared before the next piece of sodium was added. The acetylene flow was stopped at the exact moment when the blue colour disappeared after the last piece of sodium had been added (this ensured that no excess of acetylene was present in solution), and propyl iodide (41 g.) was gradually added. The reaction mixture was stirred for 4 hours, and a suspension of sodamide in liquid ammonia (150 c.c.), prepared from sodium (5·8 g.) by aid of the ferric nitrate catalyst, was then added in portions with strong cooling. The mixture was stirred for another 1 hour, and 1-chloro-4-bromobutane (41 g.) was added dropwise. The reaction was completed by stirring and cooling for another 12 hours, and ammonium chloride (15 g.) was added. The ammonia was evaporated off on the steam-bath, waterand ether were added to the residue, and the ethereal layer was washed successively with water, dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated, and distillation of the residue gave unchanged chlorobromobutane (5·3 g.) and 1-*chloronon*-5-*yne* VIII (24·2 g., 64%) as a colourless mobile liquid, b. p. 83—84°/15 mm., n_D^{18} 1·4620 (Found : C, 68·4; H, 9·9. $C_9H_{15}Cl$ requires C, 68·1; H, 9·55%).

In another experiment, propyl bromide (45 g.) was added to a solution of sodium acetylide in liquid ammonia (400 c.c.), prepared by passing acetylene through a suspension of sodamide (from sodium, 8·5 g., with the ferric nitrate catalyst). As the complete conversion of sodamide into sodium acetylide is not accompanied by a well-defined colour change, the presence of excess of dissolved acetylene in the sodium acetylide solution so formed cannot be avoided. After 3 hours' stirring, a suspension of sodamide in liquid ammonia (200 c.c.), prepared from sodium (9 g.) with the ferric nitrate catalyst, was added in portions. The cooled reaction mixture was stirred for 1 hour, 1-chloro-4-bromobutane (50 g.) was gradually added, and stirring was continued for another 4 hours. After being isolated as described previously, the product was distilled to give 1-chloronon-5-yne (3·0 g., 6%), b. p. 81°/12 mm., n_D^{17} 1·4620. The lower boiling fractions (32 g.) on redistillation gave a colourless liquid, b. p. 37—38°/10 mm., n_D^{24} 1·4461, believed to be 1-chlorohex-5-yne (formed by reaction of the chlorobromobutane with sodium acetylide, produced by the preferential reaction of the second mole of sodamide with the excess of acetylene in solution).

Undeca-1 : 7-*diyne* (III) *from* (VIII).—The chloro-compound (VIII) (2·1 g.) and a solution of sodium iodide (5 g.) in dry acetone (25 c.c.) were heated under reflux for 2 hours. The filtered solution was evaporated, the residue treated with dry ether, and the ethereal solution refiltered. This ether extract, containing the iodide (IX), was added dropwise, with stirring and cooling, to a solution of sodium acetylide in liquid ammonia (500 c.c.), prepared from sodium (3 g.) by the usual catalytic procedure. The reaction mixture was stirred for a further 3 hours, and ammonium chloride (*ca.* 10 g.) was then added. Isolation with ether gave undeca-1 : 7-diyne (0·85 g., 44%), b. p. 95°/15 mm., n_D^{21} 1·4573.

1-*Chloronon*-5(cis)-*ene* (X).—The chloro-compound (VIII) (10·52 g.) in methyl acetate (40 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (1·5 g.; 0·3% Pd), until 1 mole of hydrogen (1582 c.c. at 14°/763 mm.) had been absorbed. The filtered solution was evaporated, and the residue distilled, to give 1-*chloronon*-5-(cis)-*ene* (8·6 g.; 81%) as a colourless mobile liquid, b. p. 75°/12 mm., n_D^{17} 1·4515 (Found : C, 66·9; H, 10·8. $C_9H_{17}Cl$ requires C, 67·25; H, 10·7%). When Raney nickel was substituted for the palladium catalyst, hydrogenation proceeded considerably more rapidly to give a similar yield of (X).

Undec-7(cis)-*en*-1-*yne* (XII).—The chloro-olefin (X) (8·0 g.) was heated under reflux with a solution of sodium iodide (15 g.) in dry acetone (75 c.c.) for 15 hours. The filtered solution was evaporated, and the residue triturated with dry ether, which was again filtered. This ethereal extract, containing the iodide (XI), was added dropwise to a cooled and stirred solution of sodium acetylide (prepared from sodium, 5 g., *via* sodamide by the catalytic method) in liquid ammonia (500 c.c.). The cooled mixture was stirred for another 4 hours, and ammonium chloride (20 g.) was added. The ammonia was evaporated off on the steam-bath, and water and ether were added to the residue. The usual isolation procedure then gave *undec*-7(cis)-*en*-1-*yne* (4·6 g., 62%) as a mobile pleasant-smelling liquid, b. p. 73°/10 mm., n_D^{20} 1·4462 (Found : C, 87·5; H, 12·1. $C_{11}H_{18}$ requires C, 87·9; H, 12·1%).

Undec-7(cis)-*en*-1-*yne*-1-*carboxylic Acid* (XIII).—The hydrocarbon (XII) (4·2 g.) in dry ether (20 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·0 g.) in dry ether (50 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 2 hours, and the Grignard complex was then carbonated with solid carbon dioxide at atmospheric pressure as already described for the diacetylenic acid. After decomposition with dilute sulphuric acid, the acid fraction was isolated and gave *undec*-7(cis)-*en*-1-*yne*-1-*carboxylic acid* (3·1 g., 57%) as a colourless liquid, b. p. 116°/5 × 10^{-4} mm., n_D^{16} 1·4788—1·4790 (Found: C, 74·4; H, 9·5. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%).

N-iso*Butylundec*-7(cis)-*en*-1-*yne*-1-*carboxyamide* (XV).—The ethylenic acetylenic acid (XIII) (1·5 g.) and oxalyl chloride (3·0 g.) were heated under reflux for 30 minutes. The excess of oxalyl chloride was removed under reduced pressure, dry benzene was added to the residue, and the benzene solution concentrated, to give the crude acid chloride (XIV) as a yellow pungent liquid. This was not distilled, as, in a previous experiment, attempted distillation resulted in extensive polymerisation.

*iso*Butylamine (3·0 g.) in dry ether (10 c.c.) was added dropwise to the acid chloride in dry ether (10 c.c.) with ice-cooling and shaking. After 30 minutes, the product was isolated as described previously, and distillation gave the N-iso*butylundec*-7(cis)-*en*-1-*yne*-1-*carboxyamide* (1·3 g.) as a colourless liquid, b. p. 145—148°/10^{-3} mm., n_D^{18} 1·4876 (Found : C, 77·2; H, 11·0. $C_{16}H_{27}ON$ requires C, 77·05; H, 10·9%).

N-iso*Butylundeca*-1(cis) : 7(cis)-*diene*-1-*carboxyamide* (cis-cis-*Herculin*) (I) *from* (XV).—The *N-iso*-butyl-amide (XV) (0·35 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·04 g.; 2% of Pd) until 1 mole of hydrogen (35 c.c. at 17·5°/750 mm.) had been absorbed. The filtered solution was evaporated, whereupon distillation gave *cis*-*cis*-herculin (0·21 g.), b. p. 150—155° (bath temp.)/10^{-3} mm., n_D^{18} 1·4840.

N-iso*Butyl-lauramide.*—*cis*-*cis*-Herculin (0·21 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (46 c.c. of gas were absorbed at 21°/763 mm., equivalent to 2·2 $|=$). Removal of catalyst and solvent, followed by crystallisation of the solid residue from pentane gave *N*-*iso*butyl-lauramide as needles, m. p. 52—53° (Jacobson, *J. Amer. Chem. Soc.*, 1948, **70**, 4234, gives m. p. 51·5—52°).

Permanganate Oxidation of cis-cis-*Herculin* (I).—This oxidation was carried out with *cis*-*cis*-herculin (500 mg.) and potassium permanganate (1·7 g.) in water (50 c.c.) in exactly the manner described by Jacobson (*loc. cit.*) for natural herculin. The material not volatile in steam gave *N*-*iso*butyloxamic acid (230 mg., 82%) as needles, m. p. 105—106° (Jacobson gives 75% yield; m. p. 106—107°), and adipic acid (135 mg., 48%) as prisms, m. p. 150—152° (Jacobson gives 59% yield; m. p. 151—152°). Titration of the steam distillate with 0·1N-sodium hydroxide indicated that butyric acid had been obtained in 71% yield. It was identified as its *p*-bromophenacyl ester, m. p. 70°, undepressed on admixture with an authentic specimen (m. p. 70°).

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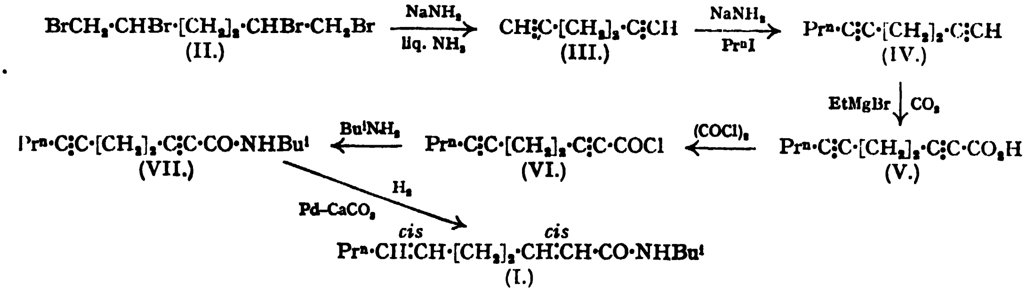
25. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part II. The Synthesis of a Geometrical Isomer of Pellitorine.*

By R. A. Raphael and Franz Sondheimer.

A geometrical isomer of the insecticide pellitorine (I; configuration about the double bonds unknown) has been synthesised by one of the methods used for the preparation of the herculin isomer described in the preceding paper. An improved preparation of dipropargyl (III) is given. The differential monoalkylation of (III), followed by carboxylation, yielded the diacetylenic acid (V), which was converted into the *N*-*iso*butyl-amide (VII). Partial hydrogenation of this gave *N*-*iso*butylnona-1(*cis*) : 5(*cis*)-diene-1-carboxyamide (*cis*-*cis*-pellitorine) (I), which however was not identical with the natural insecticide.

The root of the North African plant *Anacyclus pyrethrum* DC. has been used medicinally to stimulate the activity of the salivary glands and for the alleviation of bronchitis. The powdered root when chewed causes a persistent tingling sensation and partial insensibility of the tongue, accompanied by profuse salivation. The active principle, pellitorine, has been examined by various workers (Bucheim, *Arch. Exp. Path. Pharm.*, 1876, **5**, 455; Dunstan and Garnett, *J.*, 1895, **67**, 100; Schneegans, *Pharm. Ztg.*, 1896, **41**, 668). It was first obtained in the pure state by Gulland and Hopton (*J.*, 1930, 6), who showed it to be an *N*-*iso*butylnonadienecarboxyamide. The exact location of the double bonds in pellitorine has recently been established by Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366), who showed it to be the *N*-*iso*butylnona-1 : 5-diene-1-carboxyamide (I; configuration about the double bonds unknown). The American author also found this material (a lower homologue of herculin; cf. preceding paper) to possess insecticidal properties.

The synthesis of the *cis*-*cis*-isomer (I) has been accomplished by one of the methods employed for the preparation of the herculin isomer described in the previous paper. The starting material, dipropargyl (hexa-1 : 5-diyne) (III), had previously been obtained in rather poor yield (*ca.* 35%) by the dehydrobromination of 1 : 2 : 5 : 6-tetrabromohexane (II) with alcoholic potassium hydroxide (*inter al.*, Griner, *Ann. Chim.*, 1892, **26**, 347; Lespieau, *ibid.*, 1912, **27**, 152). Heating the tetrabromide with sodamide in light petroleum gave only very small yields of the hydrocarbon (Bourguel, *ibid.*, 1925, **3**, 233). It has been shown that sodamide in liquid ammonia is an efficient and mild dehydrobrominating agent (Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and when the tetrabromide (II) (obtained by the addition of bromine to diallyl) was treated with an excess of this reagent, the diacetylene (III) could be isolated in 56% yield.


$BrCH_2{\cdot}CHBr{\cdot}[CH_2]_2{\cdot}CHBr{\cdot}CH_2Br$
(II.)
$NaNH_2$
liq. NH_3
$CH{:}C{\cdot}[CH_2]_2{\cdot}C{:}CH$
(III.)
$NaNH_2$
Pr^nI
$Pr^n{\cdot}C{:}C{\cdot}[CH_2]_2{\cdot}C{:}CH$
(IV.)
EtMgBr
CO_2
$Pr^n{\cdot}C{:}C{\cdot}[CH_2]_2{\cdot}C{:}C{\cdot}CO_2H$
(V.)
$(COCl)_2$
$Pr^n{\cdot}C{:}C{\cdot}[CH_2]_2{\cdot}C{:}C{\cdot}COCl$
(VI.)
Bu^iNH_2
$Pr^n{\cdot}C{:}C{\cdot}[CH_2]_2{\cdot}C{:}C{\cdot}CO{\cdot}NHBu^i$
(VII.)
H_2
Pd–$CaCO_3$
cis
cis
$Pr^n{\cdot}CH{:}CH{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}CO{\cdot}NHBu^i$
(I.)

When (III) reacted first with 1·1 moles of sodamide in liquid ammonia and then with propyl iodide, the required monoalkylation product, *nona*-1 : 5-*diyne* (IV), was formed in 44% yield. The Grignard complex of (IV) was carbonated with solid carbon dioxide at atmospheric pressure, whereupon the diacetylenic *acid* (V), a crystalline solid, m. p. 87°, was formed. Although the yield obtained in this manner was very poor (*ca.* 8%), it could be increased to 63% by carrying out the reaction under pressure in an autoclave. The acid (V) was converted into the acid chloride (VI) by treatment with oxalyl chloride, excess of *iso*butylamine then giving the crystalline diacetylenic N-iso*butyl-amide* (VII). When this absorbed two moles of hydrogen in the presence of a palladium–calcium carbonate catalyst, the N-iso*butylnona*-1(cis) : 5(cis)-*diene*-1-*carboxyamide* (cis-cis-*pellitorine*) (I) was obtained as a homogeneous liquid. (The reasons for assigning the *cis*-configuration to ethylenic compounds obtained by the catalytic partial hydrogenation of acetylenes has already been given in the previous paper.)

It has been found that the second method used for the synthesis of the herculin isomer could not be applied in this case, as compounds of the type RC⋮C·CH$_2$·CH$_2$X and R·CH⁚CH·CH$_2$·CH$_2$X (where X = halogen) on treatment with sodium acetylide in liquid ammonia mainly underwent dehydrohalogenation rather than normal condensation (Sondheimer, forthcoming communication).

The pellitorine isomer (I) obtained by the method described proved to be a somewhat viscous liquid, which could not be induced to crystallise, whereas natural pellitorine is a crystalline solid, m. p. 72° (Gulland and Hopton, *loc. cit.*; Jacobson, *loc. cit.*). Moreover, although (I) had a very bitter taste, it exhibited none of the physiological properties of pellitorine described above.

That (I) differed from pellitorine solely in its geometrical configuration was confirmed by complete hydrogenation to the crystalline *N*-*iso*butylnonane-1-carboxyamide, and by potassium permanganate oxidation, whereby the three fragments (butyric, succinic, and *N*-*iso*butyloxamic acid) were isolated in yields very similar to those obtained by Jacobson (*loc. cit.*) for the natural pellitorine.

It is interesting to note the close structural similarity between the acid moiety (VIII) of pellitorine and the violet perfume, nona-2 : 6-dien-1-al (IX). Two methods for the synthesis of the latter have been developed (Ruzicka and Schinz, *Helv. Chim. Acta*, 1934, **17**, 1602; Hunsdiecker, *Chem. Ber.*, 1947, **80**, 137), and application of either of these methods should give

(VIII.) Pr$^{\text{a}}$·CH⁚CH·[CH$_2$]$_2$·CH⁚CH·CO$_2$H Et·CH⁚CH·[CH$_2$]$_2$·CH⁚CH·CHO (IX.)

the acid (VIII) in both the 1(*trans*) : 5(*trans*)- and the 1(*trans*) : 5(*cis*)-configurations. By analogy with the natural nonadienal (IX) and nonadienol (Takei *et al.*, *Bull. Agric. Chem. Soc. Japan*, 1938, **14**, 64; *Chem. Zentr.*, 1938, II, 3696; Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; Sondheimer, forthcoming publication), and with other αβ-unsaturated acids (cf. English, Bonner, and Haagen-Smit, *J. Amer. Chem. Soc.*, 1939, **61**, 3434; Lauer and Gensler, *ibid.*, 1945, **67**, 1171) the latter configuration is most probably the one present in natural pellitorine. The synthesis of this 1(*trans*) : 5(*cis*)-pellitorine by the methods indicated is now in progress in these laboratories.

EXPERIMENTAL.

Dipropargyl (*Hexa*-1 : 5-*diyne*) (III).—1 : 2 : 5 : 6-Tetrabromohexane was prepared in 95% yield by the gradual addition of the theoretical amount of bromine to a well-cooled solution of diallyl (hexa-1 : 5-diene) in ether, followed by removal of solvent under reduced pressure.

A suspension of sodamide in liquid ammonia (4 l.) was prepared from sodium (322 g., 14 moles), the ferric nitrate catalyst described by Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used to catalyse the transformation. Tetrabromohexane (704 g., 1·75 moles) in dry ether (1·6 l.) was added dropwise during 2 hours to the cooled (alcohol–carbon dioxide) and stirred suspension, which was then stirred for another 3 hours. The reaction mixture was set aside overnight without cooling, whereby most of the ammonia evaporated. (It was found advisable to allow the ammonia to evaporate before decomposing the sodio-complex, in order to minimise losses of the volatile product.) Ether, ice, and water were added to the residue, the aqueous layer was washed with ether, and the combined organic extracts were washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and then dried. The solvent (*ca.* 2·5 l.) was removed through a Dufton column; distillation of the residue through the same column gave dipropargyl (76·9 g., 56%) as a colourless liquid, b. p. 87·5—88·5°/758 mm., n_{D}^{23} 1·4380—1·4382 (Griner, *Ann. Chim.*, 1892, [6], **26**, 347, gives b. p. 85—86°). There remained a small (*ca.* 10 g.) non-volatile brown residue.

Nona-1 : 5-*diyne* (IV).—Dipropargyl (14·6 g.) in dry ether (25 c.c.) was added during 15 minutes to a cooled (alcohol–carbon dioxide) and stirred suspension of sodamide in liquid ammonia (200 c.c.), prepared from sodium (4·7 g.) by the catalytic procedure. After 1 hour's stirring, propyl iodide (40 g.) in ether (40 c.c.) was added dropwise during 30 minutes, and the cooled mixture was then stirred for a further 6 hours. Ammonium chloride (*ca.* 15 g.) was introduced, the ammonia was evaporated on the steam-bath, and the product was isolated with ether. Distillation then gave *nona*-1 : 5-*diyne* (9·9 g., 44%) as a mobile pleasant-smelling liquid, b. p. 62°/19 mm., n_{D}^{21} 1·4562—1·4565 (Found: C, 89·65; H, 10·2. C_9H_{12} requires C, 89·9; H, 10·1%).

Nona-1 : 5-*diyne*-1-*carboxylic Acid* (V).—Nona-1 : 5-diyne (4·8 g.) in dry ether (10 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·3 g.) in ether (80 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 90 minutes and then cooled in ice. It was poured on to a large excess of solid carbon dioxide in a stainless-steel autoclave, which was then sealed and allowed to attain room temperature. After 14 hours the autoclave was opened, and the solid complex decomposed with dilute sulphuric acid. More ether was added, and the ethereal layer was washed with water and sodium hydrogen carbonate solution. The latter extract was washed with ether, acidified, and again shaken with ether. This last ether extract was dried and evaporated, yielding a residue which on cooling completely solidified. Crystallisation from light petroleum (b. p. 60—80°) gave *nona*-1 : 5-*diyne*-1-*carboxylic acid* (4·15 g., 63%) as plates, m. p. 85—86° raised to 87° by further crystallisation (Found: C, 73·45; H, 7·5. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

The experiment was also carried out similarly, except that the carboxylation with solid carbon dioxide was at atmospheric pressure (cf. Part I, preceding paper). This yielded the crystalline acid (0·5 g., 8%), most of the starting material being recoverable.

*Nona-*1 : *5-diyne-*1*-carboxyl Chloride* (VI).—The acid (V) (1·4 g.) and oxalyl chloride (5·0 g.) were heated under reflux for 30 minutes. The excess of reagent was removed under reduced pressure, and distillation of the residue gave the acid chloride (1·2 g.) as a pungent yellow liquid, b. p. 95—97°/0·8 mm., n_D^{20} 1·4930. There was a considerable brown solid residue. The distillation was found to be advisable as it facilitated the purification of the product obtained in the following stage.

N-iso*Butylnona-*1 : *5-diyne-*1*-carboxyamide* (VII).—A solution of *iso*butylamine (2·0 g.) in dry benzene (5 c.c.) was added dropwise during 5 minutes to the acid chloride (VI) (1·1 g.) in benzene (5 c.c.), with ice-cooling and continuous shaking. The clear solution was set aside at room temperature overnight, and was then washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated, yielding a residue which completely solidified on cooling. One crystallisation from light petroleum (b. p. 40—60°) gave the N-iso*butylnona-*1 : *5-diyne-*1*-carboxyamide* (1·02 g.) as long needles, m. p. 72° (Found : C, 76·3; H, 9·5; N, 6·5. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·65; N, 6·4%).

N-iso*Butylnona-*1(cis) : 5(cis)*-diene-*1*-carboxyamide* (cis-cis-*Pellitorine*) (I).—The *N-iso*butyl-amide (0·81 g.) in ethyl acetate (15 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·08 g.; 5% Pd). Hydrogenation proceeded very rapidly and 2 moles of hydrogen (176 c.c. at 18°/778 mm.) were absorbed in *ca.* 5 minutes. The reaction was interrupted, the catalyst was filtered off, and the solvent was evaporated. Distillation of the residue gave cis-cis-*pellitorine* (0·61 g.) as a somewhat viscous colourless liquid, b. p. 125—126°/5 × 10^{-4} mm., n_D^{20} 1·4855—1·4857 (Found : C, 74·65; H, 11·3; N, 6·2. $C_{14}H_{25}ON$ requires C, 75·3; H, 11·3; N, 6·25%).

N-iso*Butylnonane-*1*-carboxyamide.*—*cis-cis-*Pellitorine (0·12 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (26·5 c.c. of gas were absorbed at 23°/762 mm., equivalent to 2·0 ⊨). Removal of catalyst and solvent, followed by crystallisation of the solid residue from light petroleum (b. p. 40—60°) at −40°, gave *N-iso*butylnonane-1-carboxyamide as a microcrystalline powder, m. p. 37—37·5° (Gulland and Hopton, *J.*, 1930, 6, give m. p. 36°).

Permanganate Oxidation of cis-cis-*Pellitorine* (I).—This oxidation was carried out with *cis-cis-*pellitorine (200 mg.) and potassium permanganate (750 mg.) in water (20 c.c.) in exactly the manner described by Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366) for natural pellitorine. The material not volatile in steam furnished *N-iso*butyloxamic acid (92 mg., 71%) as long needles, m. p. 103—104°, raised to 106—107° by another crystallisation (Jacobson, *loc. cit.*, gives 77% yield; m. p. 106—107°), and succinic acid (63 mg., 60%) as prisms, m. p. 186° undepressed on admixture with an authentic specimen (m. p. 189°) (Jacobson, *loc. cit.*, gives 69% yield). Titration of the steam-distillate with 0·1N-sodium hydroxide indicated that butyric acid had been obtained in 87% yield. It was identified as its *p*-bromophenacyl ester, m. p. 69° undepressed on admixture with an authentic specimen (m. p. 70°).

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26. *Complexes between Metal Salts and Long-chain Aliphatic Amines. Part I. The Complexes of Cupric Salts with Long-chain Amines.*

By A. R. BURKIN.

Complexes between cupric salts and long-chain amines are described. The chain length affects only the solubility in organic solvents and physical properties of the complexes. The acid radical controls the colour and stability of the compounds, chelation leading to relative instability. The acid radicals are covalently bound to the metal. Cupric carbonate and oxide compounds are basic and decompose chloroform on heating, giving cupric chloride complexes.

THE present work was carried out in order to study the relative stabilities, properties, and reactions of complexes of uni- and bi-valent copper salts and primary aliphatic amines with long carbon chains, dealing in particular with the effects of (*a*) the anion used, (*b*) the basicity of the amine, and (*c*) the nature of the solvent.

Water is generally used as the solvent in the study of copper complexes and it may have a considerable effect on the results obtained. In the case of cuprous compounds, this is often shown by a tendency to disproportionate, giving metallic copper and cupric ions. Bivalent copper has a great affinity for oxygen, and the properties of many cupric complexes are probably due to some extent to the partial replacement of the co-ordinating groups by water molecules. The tendency towards such aquation in the case of a salt $(MR_n)^{p+}\,X^-{}_p$ may be represented by equilibria of the types :

$$(MR_n)^{p+} \rightleftharpoons (MR_{n-1})^{p+} + R$$

$$(MR_{n-1})^{p+} + H_2O \rightleftharpoons (MR_{n-1},H_2O)^{p+}$$

and in addition the anion present may co-ordinate according to the reaction

$$(MR_{n-1})^{p+} + X^- \rightleftharpoons (MR_{n-1}X)^{(p-1)+}$$

n being the normal chemical co-ordination number of the metal M, and R representing the ionically neutral monodentate ligand. The equilibrium position of the first reaction is determined by the normal stability constant of the complex ion and, in addition, more than one R group may be lost by the complex ion, leading to further equilibria involving water and the anion. The extent to which the last two groups enter the co-ordination sphere depends on the relative co-ordinating powers of R, H_2O, and X^-, on the nature of the metal M in the general case, and also on the energies of solvation of the various groups.

King (*J.*, 1930, 2307) studied cuprammonium salts and states that there is no evidence that aquation occurs when the complexes are dissolved in water. There is little evidence that it does not occur, however. He also presents some evidence suggesting that co-ordination of anions may occur to a small extent. Reversible co-ordination of anions is well established, however, since in addition to the obvious evidence presented by the methods of preparation of many complexes of cobalt, platinum, and other metals, containing acid radicals in the complex ion or molecule, King (*J.*, 1938, 1338; 1948, 1912) has shown that in the diammino- and triamminoplatinous salts some acid radicals, normally regarded as present in the complex ions or molecules, ionise. This leads to the formation of aquated ammine ions in solution, although on crystallising, the original compounds are obtained. It is noteworthy that nitrate, sulphate, and picrate groups ionise in this way, while chloride remains in the complex molecule, diamminoplatinous chloride being practically a non-electrolyte.

In the present work the question of the influence of water does not arise, since the long-chain aliphatic amines used as ligands give complexes which are soluble in organic solvents such as chloroform, benzene, light petroleum, etc. This study of inorganic chemistry in inert organic solvents enables the properties of the actual complex molecules to be investigated and the effects of different acid radicals can thus be established.

The results obtained show that under these conditions the acid radicals are covalently bound to the copper atom and that the co-ordination number of 4 for copper is maintained. This behaviour is not observed for the copper complexes with lower amines, such as ethylamine, and ammonia, but it is believed that this is not the result of a fundamental change in the nature of the copper–acid radical links caused by changing the ligand from, say, ethylamine to *n*-octylamine, but is due to the solvents used. For example, cupric chloride with ethylamine gives complexes which are insoluble in organic solvents; the solids such as $CuCl_2(C_2H_5{\cdot}NH_2)_4$ are decomposed by water, giving a pale blue precipitate of basic cupric chloride containing a little ethylamine (or cupric hydroxide containing chloride and ethylamine which might be regarded as " adsorbed "). In aqueous ethylamine, however, the substances are soluble, and complex ions such as $[Cu(C_2H_5{\cdot}NH_2)_4]^{2+}$ may be presumed to be present. Octylamine, on the other hand, gives the *complex* $[CuCl_2(C_8H_{17}{\cdot}NH_2)_2]$, which is soluble in organic solvents and behaves as a complex molecule, but it is rapidly decomposed by water giving a pale blue precipitate containing chloride, and liberating octylamine.

All the cupric salts investigated gave bisamine complexes only, with long-chain amines, the acid radicals used being chloride, bromide, acetate, succinate, adipate, carbonate, sulphate, and that of methyl hydrogen succinate. Cupric chloride, acetate, and methyl succinate dissolve readily in a solution of 2 mols. of amine in a solvent, the bisamine complexes being precipitated on cooling to room temperature.

Cupric adipate and succinate give bisamine complexes which are unstable in solution in the absence of excess of amine. Adipic and succinic acids can form strainless rings on chelating with copper and the instability of the complexes is believed to be due to a reduction in the strength of the metal–amine bond caused by the imposition of the *cis*-configuration. The complex carbonates are also unstable and cannot be obtained without a considerable amount of associated amine carbonate.

Cupric sulphate is insoluble in solutions of the amines, but on adding the theoretical quantity of sulphuric acid to a solution of a lilac carbonate complex a pale blue precipitate of $(CuSO_4,2C_{16}H_{33}{\cdot}NH_2)$ is deposited. This *complex* is insoluble in organic solvents, concentrated solutions of amines, and molten amine. A small amount of the same compound was obtained on heating copper sulphate with hexadecylamine at 160° for about 12 hours.

Addition of nitric acid to the carbonate solution caused decomposition to free amine and cupric nitrate, no complex being formed. Thus cupric nitrate complexes do not exist, and the sulphate compounds have exceptional insolubility. This may be due to nitrate and sulphate radicals being less able to form covalent bonds to copper than the other groups used in this work. These same two anions were found by King (*loc. cit.*) to be less firmly bound to platinum than say Cl^-, tending to give aquated ions from $[Pt(NH_3)_2(NO_3)_2]$, etc.

EXPERIMENTAL.

The method used to prepare the complexes with the higher amines is essentially that of Broome, Ralston, and Thornton (*J. Amer. Chem. Soc.*, 1946, **68**, 67), the anhydrous cupric salt being dissolved in a solution of the amine in chloroform, benzene, light petroleum, etc., by boiling under reflux. On cooling, the complex separates and is purified by recrystallisation. Those authors and Ralston, Broome, Harriman, and Marcous (*J. Amer. Oil Chem. Soc.*, 1947, **24**, 307) prepared the following compounds of cupric chloride, acetate, and oleate: $CuCl_2,2R{\cdot}NH_2$; $Cu(OAc)_2,2R{\cdot}NH_2$, and $Cu(C_{17}H_{33}{\cdot}CO_2)_2,2R{\cdot}NH_2$, where R is *n*-dodecyl or *n*-octadecyl. The former group of authors (*J. Amer. Chem. Soc.*, 1946, **68**, 849) also proved spectrophotometrically that complexes such as $Cu(OAc)_2,4R{\cdot}NH_2$ do not exist in solution.

In agreement with the above authors it was found that oxygen-containing solvents such as alcohols, ethers, and ketones give ill-defined greenish products which contain solvent and are deficient in acid radicals, so that compounds containing oxygen must not be used for either the preparation or the purification of the copper–amine complexes. Apart from this restriction, all the common organic solvents may be used, the choice being controlled, very largely, by solubilities, except in the case of the cupric carbonate complexes which are unstable except in benzene solution.

The amines used were *n*-octyl-, *n*-dodecyl-, *n*-tetradecyl-, *n*-hexadecyl-, and *n*-octadecyl-amine, and there was no difference between any of the cupric complexes as far as their type is concerned. The solubilities of the complexes differed considerably, however. Like many compounds possessing long carbon chains, the cupric bisamine complexes are very slightly soluble in cold solvents, and their solubility increases enormously over a very narrow temperature range, until they seem to be infinitely soluble at a slightly higher temperature (cf. Ralston *et al.*, *J. Org. Chem.*, 1944, **9**, 102). All the complexes prepared show this effect, the critical temperature region and range differing somewhat for different solvents and being higher the longer the carbon chain.

Cupric Chloride Complexes.—Cupric chloride (2·5 g.), dried at 110°, and *n*-octylamine (5·7 g., 2 mols.) were heated under reflux with 50 ml. of chloroform until solution was complete (½ hour). On cooling, the *complex* separated as a blue powder and was purified by recrystallising twice from chloroform (Found, in air-dried specimen: Cu, 16·1; Cl, 18·0. $C_{16}H_{38}N_2Cl_2Cu$ requires Cu, 16·2; Cl, 18·0%).

The following compounds were prepared similarly: $CuCl_2,2C_{12}H_{25}{\cdot}NH_2$ (Found: Cu, 12·7; Cl, 14·0. Calc. for $C_{24}H_{54}N_2Cl_2Cu$: Cu, 12·6; Cl, 14·0%). *Tetradecylamine* complex (Found: Cu, 11·15; Cl, 12·6. $C_{28}H_{62}N_2Cl_2Cu$ requires Cu, 11·2; Cl, 12·6%). *Hexadecylamine* complex (Found: Cu, 10·2; C, 11·6. $C_{32}H_{70}N_2Cl_2Cu$ requires Cu, 10·3; Cl, 11·5%). $CuCl_2,2C_{18}H_{37}{\cdot}NH_2$ (Found: Cu, 9·5; Cl, 10·6. Calc. for $C_{36}H_{78}N_2Cl_2Cu$: Cu, 9·4; Cl, 10·5%).

Anhydrous cupric chloride (2·0 g.) was gently warmed under reflux with 50 ml. of benzene containing anhydrous ethylamine (4 g., 6 mols.). The brown solid slowly absorbed ethylamine, turning blue and then purple, no solid dissolving. A further 10 g. of ethylamine were added, and a little purple solid dissolved, giving a deep blue solution. The solid was filtered off under suction and dried in a desiccator containing anhydrous ethylamine and petroleum jelly which absorbed benzene. Exposure to air caused loss of amine, the solid turning greenish-blue but reabsorbing gaseous amine and turning purple (Found: Cu, 19·2. Calc. for $C_8H_{28}N_4Cl_2Cu$: Cu, 20·2%).

Cupric Bromide Complexes.—Cupric bromide will dissolve only in the presence of about 3—4 mols. of amine, light petroleum being the most convenient solvent since the complex does not separate well from other solvents in the presence of the excess of amine. The evidence for the composition of the cupric bromide bisamine complexes is not entirely satisfactory since the copper content cannot be determined accurately by the methods used, the results usually being low and non-reproducible. The same effects are observed with the products obtained by oxidation of cuprous bromide compounds (Part III), so the original cupric bromide is not the cause. Heating the green complexes at 100—200° in high vacuum ($< 10^{-2}$ mm.) with no air leak causes amine to condense in the cold parts of the apparatus, the complex turning brown. This residue is still soluble in organic solvents, and addition of a little amine gives the original green solid, and although this must be free from excess of amine the copper figures are still low. The complex bromides are not volatile. The molecular wieght of the *complex* ($CuBr_2,2C_{18}H_{37}{\cdot}NH_2$) determined ebullioscopically by the graphical method (Part II) in benzene is 990 ($C_{36}H_{78}N_2Br_2Cu$ requires *M*, 762). The high value compares with the value of 603 obtained for $CuCl_2,2C_{12}H_{25}{\cdot}NH_2$ as against the theoretical value of 505 (Ralston, Broome, and Thornton *loc. cit.*).

Anhydrous cupric bromide (3·0 g.) was boiled under reflux for 2 hours with octadecylamine (10·0 g., 2·8 mols.) and 50 ml. of light petroleum (b. p. 100—120°). The solid dissolved, giving a brownish solution (more amine gave green solutions) which turned green on cooling, depositing a green solid. This was recrystallised 3 times from light petroleum, the solution being filtered at 64°, and the green solid washed with several portions of fresh solvent. The product is apparently $CuBr_2,2C_{18}H_{37}{\cdot}NH_2$ (m. p. 116—117°) (Found: Cu, 6·8, 6·9; Br, 21·4, 21·4; C, 57·7; H, 10·8. $C_{36}H_{78}N_2Br_2Cu$ requires Cu, 8·3; Br, 20·95; C, 56·7; H, 10·3%). The analysis figures are the best obtained from many preparations, other amines giving such varied results that they are not quoted. After several recrystallisations a more soluble brown compound, apparently a cupric bromide complex containing less amine, could be obtained.

Cupric Acetate Complexes.—Cupric acetate was prepared by dissolving the commercial "neutral" salt in dilute acetic acid, filtering hot, cooling, and washing the crystals well with water and drying the air-dried solid *in vacuo* over phosphoric oxide until fresh desiccant extracted no more water. The anhydrous solid (1·1 g.) was boiled with octadecylamine (3·4 g.; 2·1 mols.) in 40 ml. of benzene for 30 minutes. The clear blue liquid on cooling gave a lilac solid which on recrystallising from benzene gave transparent lilac plates of $Cu(OAc)_2,2C_{18}H_{37}{\cdot}NH_2$, m. p. 89° (Found: Cu, 8·7; C, 64·6; H, 11·9. Calc. for $C_{40}H_{84}O_4N_2Cu$: Cu, 8·8; C, 66·6; H, 11·8%).

Cupric Methyl Succinate Complexes.—*Cupric methyl succinate* was prepared by boiling 50 g. of methyl hydrogen succinate with 30 g. (0·5 mol.) of cupric oxide and 50 ml. of water for 15 minutes. The considerable residue of cupric oxide was filtered off from the hot solution, which was cooled in ice, giving a mass of green crystals contaminated with excess of ester. The solid was dissolved in water with the minimum of heating, and the small amount of pale blue decomposition product filtered off from the hot solution. This was cooled rapidly in ice, and the green crystals were filtered off and dried in air and finally *in vacuo* over phosphoric oxide (Found : Cu, 19·50. $C_{10}H_{14}O_8Cu$ requires Cu, 19·50%).

Cupric methyl succinate (2·3 g.), octadecylamine (3·8 g.; 2·1 mols.) and 40 ml. of benzene were heated under reflux for 10 minutes. No solid separated from the clear blue liquid on cooling to room temperature, but on cooling in ice a blue solid separated. It was filtered off and recrystallised twice from benzene with rejection of the first third of the solid which separated in each case (this contained the excess amine). Pure *cupric methyl succinate bisoctadecylamine* was finally obtained (Found : Cu, 7·3. $C_{46}H_{92}O_8N_2Cu$ requires Cu, 7·35%).

Cupric methyl succinate bisdodecylamine was obtained similarly but was recrystallised from light petroleum (b. p. 60—80°) (Found : Cu, 9·05. $C_{34}H_{68}O_8N_2Cu$ requires Cu, 9·1%).

Cupric Succinate Complexes.—Cupric succinate was prepared by boiling cupric oxide in an aqueous solution of excess of succinic acid, filtering off the blue solid, and boiling it with more succinic acid solution. The crystals were dehydrated *in vacuo* over phosphoric oxide (Found : Cu, 35·7. Calc. for $C_4H_4O_4Cu$: Cu, 35·4%).

Cupric succinate (1·06 g.), octadecylamine (6·4 g., 4·2 mols.) and 80 ml. of benzene were heated under reflux for one hour. The boiling liquid was filtered, the filtrate cooled slowly, and the solid *complex* filtered off under suction at about 40°. It decomposed to cupric succinate on attempted recrystallisation, and amine impurity was removed by warming the lilac solid with benzene at about 45°, and filtering at that temperature. It was air-dried (Found : Cu, 8·75. $C_{40}H_{82}O_4N_2Cu$ requires Cu, 8·85%).

Cupric Adipate Complexes.—Cupric adipate was prepared as for the succinate (Found : Cu, 30·4. Calc. for $C_6H_8O_4$ Cu : Cu, 30·6%). Its *bisoctadecylamine* complex was obtained as a lilac powder by the same method as the foregoing. It is insoluble in benzene and light petroleum in the absence of excess of amine, and is decomposed by boiling or long storage with these and all other solvents. Some of the product was very carefully recrystallised from chloroform. (Found : Cu, 8·8. $C_{42}H_{86}O_4N_2Cu$ requires Cu, 8·52%). The *bisdodecylamine* complex was obtained similarly but was purified only by washing with warm benzene (Found : Cu, 11·2. $C_{30}H_{62}O_4N_2Cu$ requires Cu, 11·0%).

Cupric Carbonate Complexes.—Copper oxide and hydroxide are completely unaffected by amine solutions in the absence of carbon dioxide, but in its presence they dissolve if about 4 mols. of amine are used, lilac cupric carbonate complexes separating on cooling. Benzene is the only suitable solvent of those tried, light petroleum giving only small quantities of a green complex oxide and chloroform being decomposed, the cupric chloride bisamine complex separating. The lilac complexes, including the insoluble ethylamine complex, are of the type $(CuCO_3,2R{\cdot}NH_2)[(R{\cdot}NH_3)_2CO_3]_x$, where x is variable between 0·7 and 2. Recrystallisation alters the value of x and must be done in the presence of gaseous carbon dioxide. If the solution is too hot or not enough carbon dioxide is present, a greyish-blue solid is obtained containing more copper and less carbon dioxide but of indeterminate composition, which absorbs carbon dioxide, turning lilac. The same blue products are obtained when lilac compounds are kept over soda–lime, etc., to remove carbon dioxide. Further loss of carbon dioxide from solutions of complex carbonates causes precipitation of green solids, very difficult to filter, the solution often setting to a gel on cooling. The green substances have the composition $(CuO,2R{\cdot}NH_2)$ but are contaminated with a slight excess of amine which could not be removed by solvents. They absorb carbon dioxide, turning lilac; there is no intermediate formation of a blue solid; the dodecylamine complex absorbs carbon dioxide much more readily than does the octadecylamine compound. The composition of the lilac complexes was proved by titration of a solution of $(CuCO_3,2C_{16}H_{33}{\cdot}NH_2)[(C_{16}H_{33}{\cdot}NH_3)_2CO_3]_2$ with alcoholic hydrogen chloride, a glass electrode and saturated calomel reference half-cell being used with a Marconi battery-operated pH meter. The pH titration technique was checked by titrating $(C_{14}H_{29}{\cdot}NH_3)_2CuCl_4$ with alcoholic sodium hydroxide.

Cupric hydroxide was prepared from cupric sulphate by Bullnheimer and Seitz's method (*Ber.*, 1900, **33**, 817) but was repeatedly washed and drained by filtration under suction instead of by decantation. It was free from chloride, sulphate, and soluble hydroxy-radicals, and was dried at 70° for 2 hours.

This hydroxide (1·36 g.) and dodecylamine (10·0 g., 4 mols.) in 75 ml. of benzene were heated under reflux for 12 hours with a soda–lime tube in the top of the condenser. There was no reaction. The soda–lime tube was removed, and the solution quickly turned blue, cupric hydroxide slowly dissolving. The reaction was more rapid when the solution was kept at 65—70° instead of being boiled, and dissolution was much faster when a current of carbon dixoide washed by saturated sodium hydrogen carbonate solution was bubbled through the suspension. Traces of solids were removed by filtering the liquid hot, and on cooling a lilac solid separated. The general method of preparation was to warm the benzene suspension in an open flask on a water-bath, carbon dioxide being passed in continuously until solution was almost complete. The lilac products were recrystallised from benzene. Too low a concentration of complex, too high a temperature, and too high a vacuum in the Buchner flask caused loss of carbon dioxide, blue and finally green solids being obtained. Carbon dioxide was passed through when the lilac compounds were being redissolved.

Dodecylamine gave a lilac *complex* {Found : Cu, 7·95; C, 66·2; H, 11·8%. $(CuCO_3,2C_{12}H_{25}{\cdot}NH_2)[(C_{12}H_{25}{\cdot}NH_3)_2CO_3]_x$ containing Cu, 7·95, requires C, 64·0; H, 11·8%}. Recrystallisation from benzene gave another compound (Found : Cu, 8·20; C, 64·0; H, 11·4%).

A lilac compound was prepared from tetradecylamine but the solution was divided into two equal parts before cooling. The two crops of lilac powder were recrystallised from benzene under conditions as nearly as possible exactly similar [Found (i): Cu, 6·40; CO_3^{--}, 12·3%; Cu : CO_3 = 1 : 2·03. Found (ii) : Cu, 5·85; CO_3^{--}, 12·7%; Cu : CO_3 = 1 : 2·30. $C_{58}H_{126}O_6N_4Cu$ requires Cu, 6·13; CO_3^{--}, 11·55%].

A lilac hexadecylamine complex was prepared as usual and recrystallised once from benzene. In one case the complex was *cupric carbonate bishexadecylamine–hexadecylamine carbonate* (Found : Cu, 5·54, 5·56; CO_3^{--}, 10·3. $C_{66}H_{140}O_6N_4Cu$ requires Cu, 5·53; CO_3^{--}, 10·4%). Attempts to repeat this preparation gave compounds with varying copper contents. Heating at 75° with carbon dioxide under pressure gave a complex (Found: Cu, 5·88%).

Octadecylamine gave similar *complexes* {Found, in one case: Cu, 5·70; C, 70·5; H, 12·3. $(CuCO_3,2C_{18}H_{37}{\cdot}NH_2)[(C_{18}H_{37}{\cdot}NH_3)_2CO_3]_2$ containing Cu = 5·70 requires C, 69·9; H, 12·5%}.

Cupric hydroxide (3 g.) was warmed gently with ethylamine (large excess) in 50 ml. of benzene with a soda–lime tube in the top of reflux condenser; there was no reaction. On removal of this tube the cupric hydroxide slowly turned dark blue. When homogeneous in appearance it was filtered off under gravity, warmed gently with more ethylamine in benzene, under continuous passage of carbon dioxide, filtered off as before, washed with warm benzene, and dried in a desiccator containing anhydrous ethylamine carbonate and petroleum jelly in an atmosphere of carbon dioxide {Found: Cu, 24·3; CO_3^{--}, 31·2; Cu : CO_3 = 1 : 1·36. $(CuCO_3,2C_2H_5{\cdot}NH_2)[(C_2H_5{\cdot}NH_3)_2CO_3]_2$ containing Cu 24·3% requires CO_3^{--}, 30·3%}. The *complex* lost ethylamine and carbon dioxide readily in air, turning green.

Blue cupric carbonate complexes are described by one typical example. A lilac cupric carbonate dodecylamine complex was recrystallised from benzene after being warmed to a higher temperature than usual, with no carbon dioxide passing. A blue solid was deposited (Found: Cu, 8·60; CO_3^{--}, 7·40%): after a further recrystallisation (Found: Cu, 8·91; CO_3^{--}, 7·60%). Analysis of a different preparation gave: Cu, 9·30; CO_3^{--}, 9·05 ($C_{25}H_{54}O_3N_2Cu$ requires Cu, 12·86; CO_3^{--}, 12·14%. $C_{49}H_{108}O_3N_4Cu$ requires Cu, 7·35; CO_3^{--}, 6·94%).

Cupric oxide bisoctadecylamine (impure) was obtained by boiling a lilac carbonate complex in benzene until it completely decomposed, giving a green suspension which set to a gel on cooling. The hot suspension was centrifuged; the green solid was washed three times with hot benzene, being centrifuged each time, and was dried in a vacuum desiccator containing soda–lime, under continuous pumping (Found: Cu, 8·95; CO_3^{--}, nil. $C_{36}H_{78}ON_2Cu$ requires Cu, 10·28%).

Cupric hydroxide (1·4 g.) and dodecylamine (10 g., 4 mols.) in 40 ml. of chloroform were heated under reflux for 2 hours. The blue solution gave a dark blue solid on cooling; this was recrystallised twice from benzene–light petroleum and once from benzene, and was found to be cupric chloride bisdodecylamine (Found: Cu, 12·1; Cl, 13·6. Calc. for $C_{24}H_{54}N_2Cl_2Cu$: Cu, 12·58; Cl, 14·04%).

Potentiometric Titration.—Cupric carbonate bishexadecylamine-hexadecylamine carbonate (p. 125) (0·2100 g.) was dissolved in 15 ml. of warm benzene and a mixture of 60 ml. of benzene and 15 ml. of redistilled commercial absolute alcohol added slowly at 40°, carbon dioxide being passed through the whole time. One drop of water was added. By this method, decomposition of the complex was avoided. The solution was titrated with 0·101N-hydrogen chloride in absolute alcohol, the course of the reaction being followed by a glass electrode and a saturated calomel half-cell with a ground-glass joint flowing junction. The e.m.f. was measured by means of a Marconi battery-operated pH meter (pH scale), previously standardised by using the same electrodes in an aqueous buffer at pH 6·46. The curve obtained is shown in Fig. 1 (I). The two sharp falls at 7·5 and 11·0 ml. of acid correspond to the addition of 4 and 6 equivs. of HCl per g.-mol. of complex. There is a significant flattening of the curve when 4 ml. (2 equivs.) of acid are present. The reaction proceeds in 3 stages, identified by the experiments described below:

(1) $CuCO_3,2C_{16}H_{33}{\cdot}NH_2 + 2HCl = CuCl_2,2C_{16}H_{33}{\cdot}NH_2 + H_2O + CO_2$
(2) $(C_{16}H_{33}{\cdot}NH_3)_2CO_3 + 2HCl = 2C_{16}H_{33}{\cdot}NH_3Cl + H_2O + CO_2$
(3) $CuCl_2,2C_{16}H_{33}{\cdot}NH_2 + 2HCl = (C_{16}H_{33}NH_3)_2CuCl_4$

Stage 1. 0·194 g. of lilac complex used in the titration was dissolved in 30 ml. of benzene, and alcoholic 0·101N-hydrogen chloride (3·5 ml., 2·0 equivs.) added slowly. The blue solid separating on cooling slightly was filtered off and recrystallised from benzene (Found: Cu, 10·1; Cl, 11·4. Calc. for $C_{32}H_{70}N_2Cl_2Cu$: Cu, 10·3; Cl, 11·5%).

Stages 1 + 2. 0·193 g. of lilac complex in 30 ml. of benzene was treated with 0·101N-hydrogen chloride (7·1 ml., 4 equivs.). The blue solid obtain on filtration was recrystallised from benzene and chloroform (Found: Cu, 10·2%).

Cupric Sulphate Complex.—0·1925 g. of a hexadecylamine cupric carbonate complex containing 4·42% of Cu was titrated with 0·101N-alcoholic sulphuric acid, with vigorous stirring, the reaction being followed as before. The 0·00851 g. of Cu ≡ 2·64 ml. of the acid, and the 0·1113 g. of amine carbonate present ≡ 4·03 ml. of acid. The experimental curve (Fig. 1, II) shows a slight break between 2·6 and 2·8 ml. and a distinct break at 6·7 ml. of acid added, corresponding to the formation of cupric sulphate bishexadecylamine and amine sulphate, respectively. There is no formation of a cuprisulphate (9·3 ml.).

Anhydrous copper sulphate is insoluble in solutions of amines. The lilac hexadecylamine complex used above (1·75 g.) was dissolved in 50 ml. of benzene, and 75 ml. of alcohol added, with passage of carbon dioxide. 0·101N-Alcoholic sulphuric acid (24·1 ml., Cu : SO_4 = 1 : 1) was run in slowly with stirring, and after standing overnight the pale blue *cupric sulphate bishexadecylamine* was filtered off. It was insoluble in organic solvents and molten amine, and was purified by extracting it several times with hot benzene (Found: Cu, 9·80. $C_{32}H_{70}O_4N_2SCu$ requires Cu, 9·90%).

Anhydrous copper sulphate (0·8 g.) was heated in a tube with excess of dodecylamine at 160° (oil-bath) for 40 minutes; the white solid then turned uniformly pale blue. The excess of amine was removed by extracting 4 times with hot benzene, giving *cupric sulphate bisdodecylamine* (Found: Cu, 11·9. $C_{24}H_{54}O_4N_2SCu$ requires Cu, 12·0%).

Double Cupribromides.—Cupric bromide bisoctadecylamine (1·0 g.) was dissolved in benzene, and excess of hydrobromic acid in aqueous alcohol added. Alcohol was added to the violet solution until the water which settled out redissolved. Dark violet *bisoctadecylamine cupribromide* which separated on cooling was filtered off and recrystallised from alcohol–benzene (Found: Cu, 6·85; Br, 34·3. $C_{36}H_{80}N_2Br_4Cu$ requires Cu, 6·90; Br, 34·7%).

Bistetradecylamine cupribromide (Found: Cu, 7·90. $C_{28}H_{56}N_2Br_4Cu$ requires Cu, 7·85%) and *bis-*

octylamine cupribromide (Found: Cu, 9·80. $C_{16}H_{40}N_2Br_4Cu$ requires Cu, 9·91%) were prepared similarly.

Double Cuprichlorobromides.—Alcoholic hydrogen chloride was added to a solution of cupric bromide bisoctadecylamine (1·0 g.) in benzene until the colour was orange. On standing, orange yellow ***bisoctadecylamine cuprichlorobromide*** separated and was recrystallised from benzene–alcohol (Found: Cu, 7·55. $C_{36}H_{80}N_2Cl_2Br_2Cu$ requires Cu, 7·60%). ***Bisoctylamine cuprichlorobromide*** was prepared similarly (Found: Cu, 11·30. $C_{16}H_{40}N_2Cl_2Br_2Cu$ requires Cu, 11·45%). The same orange yellow solids were obtained by treating the cupric chloride bisamine complexes with alcoholic hydrogen bromide. Excess of hydrogen bromide gave the violet cupribromides; and excess of hydrogen chloride with the cuprichlorobromides gave the yellow cuprichlorides.

FIG. 1.

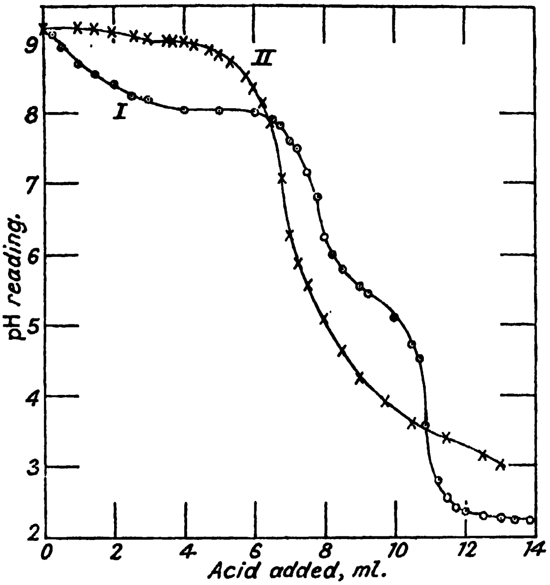
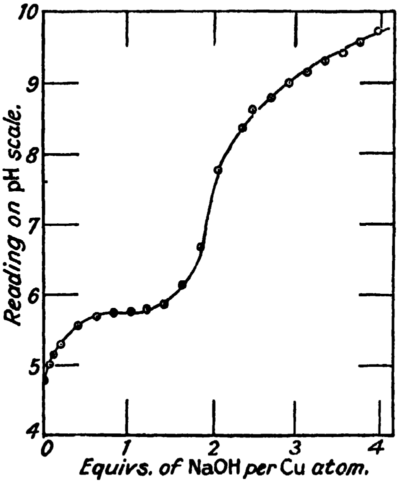


FIG. 2.



Double Cuprichlorides.—These were obtained by the methods of Ralston *et al.* (*loc. cit.*). Bistetradecylamine cuprichloride (0·1944 g.) in pure methanol (150 ml.) was titrated with 0·118N-aqueous sodium hydroxide, the glass electrode assembly described under cupric carbonate complexes being used. The curve (Fig. 2) shows a sharp break when 2 equivs. of alkali are added, confirming the formulation as a double salt and the applicability of the glass electrode under such conditions.

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UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, July 1st*, 1949.]

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27. *Complexes between Metal Salts and Long-chain Aliphatic Amines. Part II. The Complexes of Cuprous Halides with Long-chain Aliphatic Amines.*

By R. G. WILKINS and A. R. BURKIN.

Co-ordination compounds of cuprous salts (CuX) with long-chain aliphatic amines have been prepared and their structures investigated (*a*) by molecular-weight determinations and (*b*) by a study of their reactions. Cuprous chloride, bromide, and iodide form tetrameric monoamine complexes, $(CuX,R{\cdot}NH_2)_4$. Cuprous bromide forms also bisamine complexes which have dimeric bridged structures $(CuBr,2R{\cdot}NH_2)_2$ at low temperatures (freezing benzene) but dissociate into the monoamine complex and free amine at higher temperatures, the solid bisamine complex separating again on cooling. The preparation of the chloride and bromide was carried out in an oxygen-free atmosphere. Reaction between the monoamine complexes and pyridine gave, in all cases investigated, the cuprous halide–pyridine complex of empirical formula (CuX,C_5H_5N).

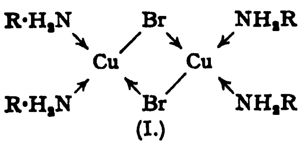
THERE is no work reported on complexes formed by co-ordination of higher primary aliphatic amines with cuprous salts. The amines chiefly used in the present work were *n*-octadecylamine, *n*-dodecylamine, and *n*-octylamine, hexadecylamine being used in a few cases where the fact that the stabilities and solubilities of its complexes are intermediate between those of the octadecyl- and the dodecyl-amine was of particular value. Cuprous chloride, bromide, and iodide were the metallic salts studied.

When cuprous chloride or bromide is added to a solution of about 2 equivs. of an amine in, for example, hot light petroleum, a mixture of blue and green, amine-containing, oxidation products is obtained. If, however, the reaction is carried out in the absence of oxygen, the cuprous salt gradually dissolves to give a green solution, which on cooling deposits a complex as a fine white or very pale green powder. A simple apparatus was devised for filtering off these compounds in the absence of air (see p. 130).

Cuprous iodide complexes are stable in air and are formed when cuprous iodide is dissolved in a hot solution of the amine in light petroleum, benzene, etc. The hexa- and octa-decylamine *complexes* are white crystalline solids. The *compounds* with lower amines are extremely soluble in the presence of the excess of amine necessary for their preparation, and either (*a*) cooling in ice–salt or (*b*) evaporation of the solution *in vacuo* merely gives the complex contaminated with the excess of amine. The pure solids are insoluble in all the usual organic solvents, but in the presence of a trace of free amine, they dissolve readily, giving red solutions, which turn colourless on prolonged heating, but regain their red colour on cooling. Molecular weights were determined by observing the boiling point of the solvent containing a trace of the amine present in the complex and treating this as the " solvent," the elevations due to the amine and complex being additive as long as no interaction occurs. With larger concentrations of amine, the amount present had an effect on the elevation, as is described below.

Cuprous chloride and iodide formed only monoamine *complexes* with the empirical formulæ ($\mathrm{CuCl,R{\cdot}NH_2}$) and ($\mathrm{CuI,R{\cdot}NH_2}$), although almost 2 mols. of amine per atom of copper were necessary for their preparation. Cuprous bromide formed a monoamine *complex*, ($\mathrm{CuBr,R{\cdot}NH_2}$), if one mol. of amine was used, but in the presence of two mols. of amine, a bisamine *complex* ($\mathrm{CuBr,2R{\cdot}NH_2}$) was formed.

No question arises as to the co-ordination number of copper for the cupric salt complexes (see Part I), it being 4 for all complexes examined. The empirical formula of the cuprous halide complexes would indicate co-ordination numbers for copper of both 2 (monoamine complex) and 3 (bisamine complex). In all cases examined, however, polymerisation occurs and the usual stable co-ordination number of 4 is attained. The bisamine complexes of cuprous bromide were shown by molecular-weight determinations in freezing benzene to have a dimeric, presumably bridged, structure (I; R = $\mathrm{C_{12}H_{25}}$ and $\mathrm{C_8H_{17}}$). The monoamine complexes were shown to have a tetrameric structure, as is described later. It is well established that halogen atoms can act as " bridging " groups between metallic atoms (for summary of work, see Mann, *Ann. Reports*, 1938, **35**, 151).



(I.)

In boiling benzene solution the molecular weight found for the bisamine complexes did not correspond to either a monomeric or a dimeric structure. The observed elevation of boiling point did, however, correspond closely to the observed and calculated values caused by an equimolecular mixture of monoamine complex and amine. The same phenomenon was observed in *n*-hexane also. It is concluded therefore that at these slightly higher temperatures, the bisamine complex dissociated into the monoamine complex and free amine, but on cooling the solution the bisamine complex was precipitated again :

$$\begin{tikzcd} 2(\mathrm{CuBr,2R{\cdot}NH_2})_2 \arrow[r, shift left] & (\mathrm{CuBr,R{\cdot}NH_2})_4 + 4\mathrm{R{\cdot}NH_2} \arrow[l, shift left] \arrow[d, "\mathrm{py}"] \\ & 4(\mathrm{CuBr,py}) + 4\mathrm{R{\cdot}NH_2} \end{tikzcd}$$

Further evidence supporting this idea of dissociation is that when treated with 1 equiv. of pyridine in hot solvents, the bisamine complexes form monopyridinocuprous bromide, the same compound as is obtained when the monoamine complex is treated with pyridine.

The molecular weights of the monoamine complexes had to be determined ebullioscopically because of their insolubility in cold solvents. Cottrell's apparatus was used and a similar apparatus containing the solvent alone was employed as " reference " thermometer. This method of eliminating the influence of the barometer is more convenient and decidedly more accurate than any method involving barometer reading and the application of a correction. The determinations were carried out in a small, draught-free room, out of the sunlight, and the precautions mentioned by Washburn and Read (*J. Amer. Chem. Soc.*, 1919, **41**, 729) were observed. The values for the boiling points were extremely steady and reproducible under these conditions, although the method is very sensitive to outside disturbances, so that any rapid movements by the observer appreciably altered the thermometer readings. In order to correct for the amount of solvent refluxing in the apparatus and present as vapour, and to smooth out the irregularities of individual readings, the solutions were progressively diluted and a number of observations made.

It can easily be shown that

$$C = 1000kC_1/\mathrm{d}T \, . \, M + x \qquad (1)$$

where C is the weight of solvent introduced into the apparatus, C_1 is the weight of solute, and x is the weight of solvent " refluxing "—a constant depending on the size of the apparatus. From (1), the graph of the weight of solvent plotted against the reciprocal of the elevation is a straight line, of slope $1000kC_1/M$. The validity of the argument depends on the fact that the molecular weight is fairly constant over a range of concentrations. The straight lines obtained for a number of complexes when this graph is plotted support this contention.

All the cuprous halide monoamine complexes $(\mathrm{CuX,R{\cdot}NH_2})_x$ examined had values for x between 2·9 and 3·3. Their structures are presumably analogous to those of the complexes formed between cuprous iodide and trialkyl-phosphines or -arsines of empirical formulæ CuI,P(or As)R_3; *X*-ray analysis of triethylarsine–cuprous iodide showed that the true molecule was $(\mathrm{CuI,AsEt_3})_4$ (Mann, Wells, and Purdie, *J.*, 1936, 1503). Mann, in addition, carried out a series of molecular-weight determinations on different members of the arsine and phosphine series in various solvents. Values of x in the polymer $(\mathrm{CuI,PR_3})_x$ were found in nearly all cases to lie between 3 and 4. It is possible that the low values of x are due to an inherent error in the molecular-weight determinations such as non-ideality of solution, the use of approximate formulæ, etc. It seems unlikely, however, that such a large and consistent difference is due to those causes and the more probable explanation is that some type of dissociation occurs in the solution.

Mann suggested that it was of the type $(\mathrm{R_3P,CuI})_4 \rightleftharpoons 4(\mathrm{R_3P,CuI})$, leading to a bicovalent cuprous complex. We have obtained, however, a certain amount of evidence for the following type of dissociation, at least with the cuprous iodide–amine complex:

$$(\mathrm{CuI,C_{18}H_{37}{\cdot}NH_2})_4 \rightleftharpoons (\mathrm{CuI,}\overline{1-x}\mathrm{C_{18}H_{37}{\cdot}NH_2})_4 + 4x\mathrm{C_{18}H_{37}{\cdot}NH_2} \qquad (2)$$

Thus we suggest that in hot solvents a small amount of amine splits off from the complex tetramer, but leaves the main bridged structure intact, a small proportion of the copper atoms momentarily having no amine attached. On cooling, the amine recombines once more and the original complex separates out. Quite a small degree of dissociation of this type, less than 10% of the amine molecules splitting off, would account for the observed results. The evidence for the type of dissociation postulated is as follows.

(1) Pure cuprous iodide–octadecylamine complex (compound *A*), was heated under reflux for about an hour in *n*-hexane in the presence of a small amount of dodecylamine. If octadecylamine had split off at all there should be competition between it and the dodecylamine when recombination occurred, and the product obtained on cooling and filtering (compound *B*) should contain dodecylamine and so have a higher copper content and lower carbon and hydrogen contents than the original compound *A*. Thus there is no question of any changes in analysis figures being due merely to contamination with excess of amine. The results obtained are given below and clearly indicate that a replacement of this type has occurred:

	$(\mathrm{CuI,C_{18}H_{37}{\cdot}NH_2})_4$ requires:	Compound *A*, found:	Compound *B*, found:
C, %	47·0	46·5	45·5
H, %	8·5	8·35	8·05
Cu, %	13·8	13·85	14·25

(2) When the molecular weight of the complex was determined in the presence of different amounts of octadecylamine, the observed value increased (corresponding to a decrease in the degree of dissociation) as the ratio of the amount of added amine to the amount of complex was increased. This would be expected, as the added amine would force the reaction (2) from right to left.

(3) On boiling a suspension of the pure complex in light petroleum in an open vessel for a few minutes, the solid lost a small amount of amine (which is slightly volatile in the solvent vapour), the copper content of the solid increasing from 13·85 to 14·2%. On recrystallising this from light petroleum containing just enough octadecylamine to make it soluble, the pure monoamine complex was obtained once more.

(4) Dissociation of this type is often encountered with co-ordination compounds of many different types. Thus most ammonia–cupric salt complexes lose ammonia very readily in air, and certain organic arsine complexes with metal salts are highly dissociated even in freezing benzene solution and smell strongly of the arsine, particularly the complexes of $IrCl_3$ with aryldialkylarsines (Dwyer and Nyholm, *J. Roy. Soc. N.S.W.*, 1944, **77**, 116; 1946, **79**, 121). Kharasch *et al.* (*J. Amer. Chem. Soc.*, 1938, **60**, 882) obtained an approximate molecular weight of 409 for the styrene–$PdCl_2$ complex by the depression of the f.p. of benzene. This is intermediate between 282 for the monomeric and 564 for the dimeric form of ($PdCl_2,C_6H_5{\cdot}CH{:}CH_2$) which should, by analogy with the $PtCl_2$ complex, be a bridged molecule. Instead of postulating splitting of the bridge, the value can be explained by assuming partial dissociation into free styrene.

We do not suggest that this type of dissociation explains all the observed phenomena of this type, for in the case of the cuprous iodide–trialkylarsine complexes the liberated trialkylarsine might be expected to oxidise easily and so lead to irreversible dissociation and decomposition of the complexes, which does not occur. Also, there is some evidence that dissociation into monomeric units also occurs. In the case of the reversible dissociation of the cuprous bromide bisamine complexes—presumably bridged dimers—into amine and cuprous bromide monoamine complexes—tetramers—it is difficult to see how the reaction can proceed except *via* the bicovalent monomeric units. As is shown in Part III, however, the mechanisms of reactions involving this type of complex in non-aqueous solvents are not clear, and dissociation giving free anions may also occur.

As mentioned above, the amine was readily replaced by a stronger co-ordinating group. Pyridine gave complexes with very low solubilities in organic solvents, thus making the determination of their molecular weights impossible. The compound obtained when cuprous iodide–amine complexes were treated with pyridine had an empirical formula (CuI,C_5H_5N). Varet (*Compt. rend.*, 1891, **112**, 391) obtained the same substance as small yellow crystals by treating cuprous iodide with pyridine; when treated with ether, the substance became white, and when exposed to air, it became green and then brown, as observed by Varet (*loc. cit.*).

The monopyridinocuprous chloride complex, empirical formula ($CuCl,C_5H_5N$), was obtained as a light yellow solid which rapidly turned green on exposure to air. In contrast to these substances, *monopyridinocuprous bromide* ($CuBr,C_5H_5N$) was a white microcrystalline solid which showed no tendency to decompose and was extremely stable. This compound is not reported in the literature but $CuBr, 2C_5H_5N$ is a well-known golden-green crystalline solid, decomposing rapidly in air (Varet, *Compt. rend.*, 1897, **124**, 1156; Marukhyan, *J. Gen. Chem. Russia*, 1940, **10**, 917).

The solubility of all the cuprous halide complexes in organic solvents decreased as the chain length of the amine involved increased. The cuprous chloride and bromide complexes, initially white solids, deepened in colour on storage in air, finally becoming a dark green. Their solutions, on boiling in air, undergo decomposition, and smell strongly of the amine.

EXPERIMENTAL.

General Method of Preparation of Complexes in an Inert Atmosphere.—In the preparation of all cuprous chloride and bromide complexes with amines, the same general method was employed. Variations in the reaction conditions are noted in the separate details of each experiment.

The whole apparatus (Fig. 1) was disconnected at the ground glass joint *A*, and the Buchner flask, funnel, and inlet tube were filled with the solvent to be used in the reaction. This was then displaced by passing a stream of nitrogen through the side-arm of the flask *B*, and allowing the solvent to pass out of the tube *C*. The side-arm and tube were closed and this portion of the apparatus was then placed on one side. The cuprous salt was placed in the reaction vessel *D*, and a stream of nitrogen was passed through the inlet tube *E* for about 15 minutes; this clears out any residual oxygen in the apparatus. The amine, dissolved in the solvent, was then added from the tap-funnel *F*, and the reaction allowed to continue until all the cuprous halide had dissolved (which indicated that the reaction was now complete), the nitrogen stream being continued meanwhile. The solution was cooled, and the complex then separated at a temperature which depended on the cuprous salt and amine used. The resultant solid was then filtered off in an atmosphere of nitrogen. The two separated parts were connected (as shown in Fig. 1), and the side-arm *B* connected to the water-pump. The filter-pump was then turned on, and the ground-glass joint *A* revolved 180°, whereupon the solid and solvent passed, *via* the glass joint and tubing, into the Buchner funnel. The solid was washed with solvent added from the tap-funnel *F*, and the precipitate then sucked dry for about 10 minutes. The Buchner funnel and precipitate were finally transferred quickly to a vacuum desiccator for final drying.

Determination of Molecular Weights.—Since the chloride and bromide complexes decomposed in air, when these complexes were used, the apparatus was filled with nitrogen, which had been washed by alkaline pyrogallol, dried by concentrated sulphuric acid, and saturated with solvent vapour. A slow stream of nitrogen was passed into the Cottrell's apparatus at the top of the condenser throughout the determination, and the gas led away through about 4 feet of narrow tubing (2 mm.) to minimise back diffusion of air. The values obtained for the molecular weights are recorded below in separate sections, the graph number referring to Fig. 2.

In all the preparative work described below, light petroleum (b. p. 60—80°) was used, although the preparation of the complexes could also be carried out in other organic solvents, *e.g.*, benzene, in which they were much more soluble, the temperature of separation being correspondingly lower.

I. *Preparation of Cuprous Chloride Complexes.—With octadecylamine.* Cuprous chloride (0·9 g., 1 mol.) was heated with 100 ml. of light petroleum containing octadecylamine (5·0 g., 2·05 mols.) for an hour at 70—80°. The complex formed was soluble above about 67°, and the green solution formed was cooled to 55° and filtered. A light green solid *complex* was obtained, which turned dark green when left in air for about 10 days (Found: Cu, 17·34, 17·36, 17·24. $C_{18}H_{39}NClCu$ requires Cu, 17·24%). The analytical figures are for three separate preparations.

With dodecylamine. Cuprous chloride (1·3 g., 1 mol.) was heated with dodecylamine (5·0 g., 2·05 mols.) in 100 ml. of light petroleum for 20 minutes at 60—65°. The cuprous chloride dissolved and gave a dark green solution, which was filtered at about 40°, at which temperature the *complex* separated in large quantities. A white solid, it turned distinctly green within an hour (Found: C, 49·7; H, 9·5; Cu, 22·2; *M*, 2·9% solution in benzene, 590; 5·7% solution in benzene, 640. $C_{48}H_{108}N_4Cl_4Cu_4$ requires C, 50·7; H, 9·6; Cu, 22·4%; *M*, 1137).

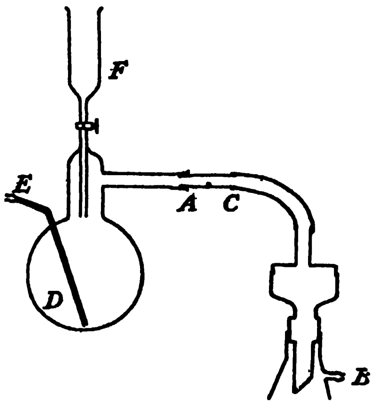


FIG. 1.

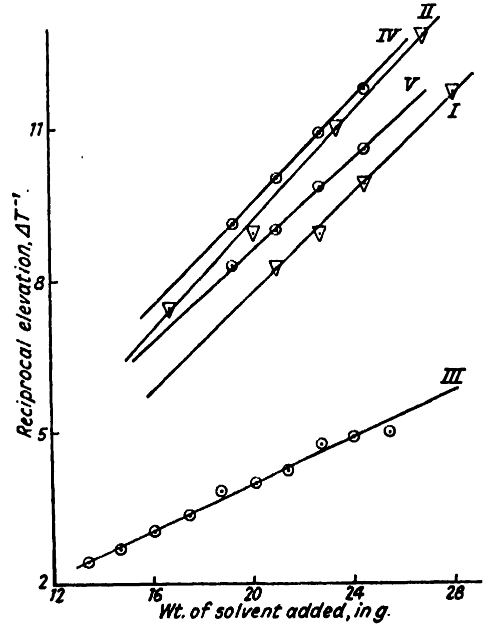


FIG. 2.

With octylamine. Cuprous chloride (1·2 g., 1 mol.) was treated with octylamine (3·2 g., 2·04 mols.) in 60 ml. of light petroleum at 60° for 15 minutes. A green solution was formed and this deposited a white solid on cooling, which must be a complex since octylamine is a liquid at these temperatures. Several attempts were made to filter it, but only a blue-green solid mixture was obtained.

With pyridine The solution of cuprous chloride–octylamine in light petroleum, obtained as above, was treated with an excess of pyridine (1·0 g., 1·04 mols.). A yellow oil formed at the bottom and solidified on cooling to a yellow solid, which was filtered off in air. The yellow crystalline solid, on exposure to air, quickly turned green.

II. *Preparation of Cuprous Bromide Complexes.—With octadecylamine.* (i) Cuprous bromide (1·0 g.) was warmed with octadecylamine (2·0 g., 1·06 mols.) in 100 ml. of light petroleum at 55° for 20 minutes. The *complex* was filtered off at 20°. A white solid, it became dark green fairly quickly (Found: Br, 19·3; Cu, 15·45. $C_{18}H_{39}NBrCu$ requires Br, 19·35; Cu, 15·4%).

(ii) Cuprous bromide (0·77 g.) was treated with octadecylamine (3·0 g., 2·07 mols.) dissolved in 100 ml. of hot light petroleum. All the salt had dissolved in 10 minutes at 58°. The *bisamino*-complex was filtered off at about 50°. A white solid, it changed to a green solid very slowly (Found: Br, 11·8; Cu, 9·4. $C_{36}H_{78}N_2BrCu$ requires Br, 11·7; Cu, 9·3%).

With dodecylamine. (i) Cuprous bromide (1·0 g.) was warmed with dodecylamine (1·35 g., 1·05 mols.) in 100 ml. of light petroleum at 35—40° for 10 minutes; a light green solution was obtained. On cooling to 16°, the *complex* separated and was filtered off. The white solid quickly became green [Found: Br, 24·2; Cu, 19·3; *M*, 2·2% in hexane, 1970; 5·6—8·0% in hexane, 2040; 3·0—4·8% in benzene, 995 (see Fig. 2, I). $C_{78}H_{108}N_4Br_4Cu_4$ requires Br, 24·3; Cu, 19·3%; *M*, 1315]. The graph obtained in *n*-hexane was not a straight line, indicating a change in *M* on dilution. The high value is difficult to interpret.

(ii) Cuprous bromide (1·0 g.) was warmed with dodecylamine (2·7 g., 2·1 mols.) in 150 ml. of light petroleum at 45°; it dissolved within 5 minutes, and the *complex* began to separate at 38°. It was filtered off at 30°. The white solid slowly became green [Found: Br, 15·5; Cu, 12·4; *M* (cryoscopic), 2·9% in benzene, 1020; 2·8% in benzene, 1121; *M* (ebullioscopic), 3·9—7·5% in hexane, 650 (Fig. 2, III), 6·4% in benzene, 445. $C_{48}H_{108}N_4Br_2Cu_2$ requires Br, 15·5; Cu, 12·4%; *M*, 1040]. The ebullioscopic molecular-weight determinations in hexane and in benzene correspond closely to that required for an equimolecular mixture of the monoamine complex and amine.

With octylamine. (i) Cuprous bromide (1·0 g.) was treated with octylamine (1·0 g., 1·1 mols.) in 50 ml. of light petroleum at 25°. After about 5 minutes the copper salt had dissolved and the green solution was cooled in ice–salt. A white solid separated at −10°. It was filtered off and washed with ice-cold light petroleum. Little solid was obtained, it having apparently redissolved; it was very dark green.

(ii) Cuprous bromide (1·0 g.) was warmed with octylamine (2·0 g., 2·2 mols.) in 100 ml. of light petroleum. On warming above 40° for about 10 minutes, the salt dissolved to form a complex which gave a green solution. On cooling, the *complex* began to separate at 34° as a silvery-white solid [Found: Br, 19·65; Cu, 15·95; *M* (cryoscopic), 3·1% in benzene, 891. $C_{32}H_{76}N_4Br_2Cu_2$ requires: Br, 19·9; Cu, 15·8%; *M*, 804].

With pyridine. Pyridine (0·35 g., 1·1 mols.), dissolved in warm light petroleum, was added to a solution of cuprous bromide bisdodecylamine (2·0 g.) dissolved in 40 ml. of light petroleum at 40°. A feathery crystalline solid was deposited and filtered off while warm. It was washed with warm light petroleum and recrystallised from 20—30 ml. of light petroleum containing a little pyridine. A fluffy solid, the *complex* darkened rapidly at 130° without melting (Found: C, 26·9; H, 2·2; N, 6·8; Cu, 28·9. C_5H_5NBrCu requires C, 27·0; H, 2·3; N, 6·3; Cu, 28·6%).

III. *Preparation of Cuprous Iodide Complexes.—With octadecylamine.* Octadecylamine (0·95 g., 1·34 mols.), dissolved in 15 ml. of hot light petroleum, was added to a suspension of cuprous iodide (0·5 g., 1 mol.) in 10 ml. of hot light petroleum. Within about 15 minutes at 65°, in the air, the cuprous iodide had dissolved, giving a deep-red solution, which on continued heating under reflux changed to an almost colourless solution. This was then cooled to about 30°; a very light-coloured solid separated, which was filtered off, washed with warm light petroleum, and recrystallised twice from light petroleum. A white feathery crystalline *complex*, m. p. 98°, was obtained [Found: C, 46·5; H, 8·35; Cu, 13·8; *M*, 3·8—6·1% in hexane, 1492 (Fig. 2, II); 3·8—5·3% in benzene, 1332 (Fig. 2, IV). $C_{72}H_{156}N_4I_4Cu_4$ requires C, 47·0; H, 8·5; Cu, 13·8%; *M*, 1840].

With hexadecylamine. Hexadecylamine (2·8 g., 1·46 mols.) was heated under reflux with cuprous iodide (1·5 g., 1 mol.) in 60 ml. of light petroleum. The resulting colourless solution was cooled in a refrigerator and a light straw-coloured *complex* separated, which was filtered off and washed with cold light petroleum. Recrystallisation from 30 ml. of light petroleum yielded a pale yellow, microcrystalline solid [Found: C, 44·0; H, 8·3; Cu, 14·8; *M*, 4·0—6·1% in benzene, 1335 (Fig. 2, V). $C_{64}H_{140}N_4I_4Cu_4$ requires C, 44·5; H, 8·2; Cu, 14·7%; *M*, 1728].

With pyridine. Tetrakis(cuprous iodide octadecylamine) (1 g., 1 mol.) was dissolved in 50 ml. of light petroleum containing a small amount of octadecylamine. To the hot solution, pyridine (0·18 g., 1·05 mols.) was added. A precipitate of light feathery crystals was slowly formed, and was filtered off while warm. On exposure to air, these commenced to turn light green, but when they were washed with ether, a white solid was obtained (Found: Cu, 23·6. Calc. for C_5H_5NBrCu: Cu, 23·6%). The reaction was repeated with a solution of cuprous iodide dodecylamine in the presence of excess of dodecylamine; a similar result was obtained. The final solid was washed with ether as before (Found: Cu, 23·7%). Several other reactions have been carried out on a solution of the complex between cuprous iodide and dodecylamine in solution (see Paper III) without the isolation of the solid complex.

UNIVERSITY COLLEGE, SOUTHAMPTON.

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28. *Complexes between Metal Salts and Long-chain Aliphatic Amines. Part III. The Oxidation of Copper*(I) *Complexes to Copper*(II) *Complexes.*

By R. G. WILKINS and A. R. BURKIN.

Cuprous halide complexes with long-chain amines and with pyridine, having empirical formulæ CuX,Z, undergo aerial oxidation and in the presence of amine salts, Z,HX, form the corresponding cupric halide complexes, $CuX_2,2Z$, X representing the halogen atom and Z the ligand. The effect of changing X and Z is studied. The oxidation leads to the formation of hitherto undescribed complexes of cupric iodide with amines, $CuI_2,2R{\cdot}NH_2$. The mechanism of the reactions is not known.

AN interesting oxidation reaction, involving the cuprous salt amine complexes (Part II) and the cupric salt amine complexes (Part I) has been discovered and investigated. If tetrakis-[cuprous chloride (or bromide) monoamine], dissolved in a non-hydroxylic solvent such as benzene, chloroform, or *n*-hexane, was heated under reflux with the corresponding amine hydrochloride (or hydrobromide), then aerial oxidation occurred and a cupric chloride (or bromide) amine complex was formed ($R = C_8H_{17}$, $C_{12}H_{25}$, or $C_{18}H_{37}$; X = Cl or Br):

$$(CuX,R{\cdot}NH_2)_4 + 4R{\cdot}NH_3X\ (+\ 2O) \longrightarrow 4CuX_2,2R{\cdot}NH_2\ (+\ 2H_2O) \quad . \quad . \quad . \quad (A)$$

An analogous reaction was observed with the cuprous iodide amine complexes but it was very much slower and less complete, especially with the higher amines, *e.g.*, octadecylamine. These compounds are an interesting example of the stabilisation of an unusual valency state by co-ordination (cf. the formation of cupric iodide complexes with ethylenediamine; Morgan and Burstall, *J.*, 1926, 2018).

This type of oxidation reaction was shown to be fairly general for univalent copper salt complexes with amines. If the complex formed between one molecule of cuprous halide and one molecule of pyridine was treated with the corresponding pyridine salt, then dipyridinocupric halide was formed (X = Cl, Br, or I; py = pyridine):

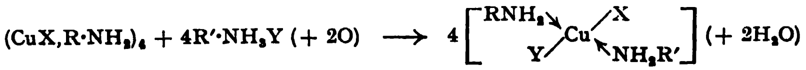
$$2(\mathrm{CuX,py}) + 2\mathrm{py,HX}\ (+\ \mathrm{O}) \longrightarrow 2\mathrm{CuX_2,2py}\ (+\ \mathrm{H_2O}) \quad . \quad . \quad . \quad . \quad . \quad (\mathrm{B})$$

(1) X = Cl. Dipyridinocupric chloride, $CuCl_2,2C_5H_5N$, is well known. Cox, Sharatt, Wardlaw, and Webster (*J.*, 1936, 129) prepared it in a number of ways in an unsuccessful attempt to obtain the *cis*-form. The product of this oxidation reaction was a blue microcrystalline solid, which recrystallised from methyl alcohol as fine, pale blue needles, exactly as described by Cox *et al.*, and was, without doubt, the *trans*-compound also.

(2) X = Br. The product of the oxidation reaction, dipyridinocupric bromide, $CuBr_2,2C_5H_5N$, was obtained by Pfeiffer and Pimmer (*Z. anorg. Chem.*, 1905, **48**, 98) as green needles, by direct reaction betweeh the components.

(3) X = I. The reaction was extremely slow, and although it is believed (from colour changes of the solutions) that a small amount of oxidation occurred, no pure dipyridinocupric iodide was obtained, and large amounts of unchanged reactants were recovered.

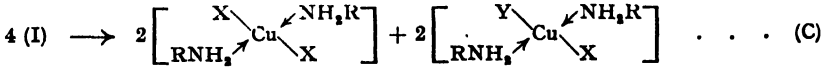
By the use of this reaction, it was hoped to prepare a compound of the form (I), by an oxidation of the general type:



$$(\mathrm{CuX,R{\cdot}NH_2})_4 + 4\mathrm{R'{\cdot}NH_3Y}\ (+\ 2\mathrm{O}) \longrightarrow 4\left[\begin{matrix}\mathrm{RNH_2} & & \mathrm{X}\\ & \mathrm{Cu} & \\ \mathrm{Y} & & \mathrm{NH_2R'}\end{matrix}\right] (+\ 2\mathrm{H_2O})$$

(I.)

The investigation was divided into two stages: (i) changing the anion and using the same amine, and (ii) changing the amine and using the same anion. In reactions of type (i), disproportionation occurred and two products were formed (X = Cl, Y = Br or OAc; X = Br, Y = Cl or OAc; X = I, Y = Cl or OAc):

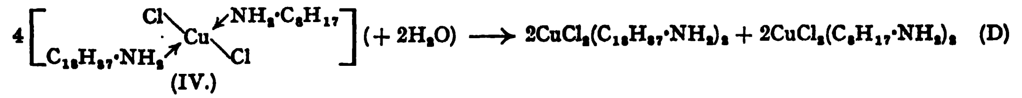


$$4\ (\mathrm{I}) \longrightarrow 2\left[\begin{matrix}\mathrm{X} & & \mathrm{NH_2R}\\ & \mathrm{Cu} & \\ \mathrm{RNH_2} & & \mathrm{X}\end{matrix}\right] + 2\left[\begin{matrix}\mathrm{Y} & & \mathrm{NH_2R}\\ & \mathrm{Cu} & \\ \mathrm{RNH_2} & & \mathrm{X}\end{matrix}\right] \quad . \quad . \quad . \quad (\mathrm{C})$$

(II.) (III.)

Possibly the intermediate compound (I) is initially formed but this extremely quickly disproportionates to the products (II) and (III). The mechanism of the reaction is not clear, but must involve the breakage of a metal–halogen (or a metal–acetate) covalent bond. The two ways of effecting this are *via* (*a*) free radicals and (*b*) ions. The former is excluded since no halogenobenzene or phenyl acetate is formed when the reaction is carried out in benzene, unless it is postulated that the free radicals react much more quickly with each other than with benzene. Therefore the reaction involving ions must be explained on the idea that a small equilibrium concentration of ions is present in the non-polar solvents benzene or *n*-hexane. It is hoped to carry out conductivity measurements on the system in an attempt to detect such ions.

Broome, Ralston, and Thornton (*J. Amer. Chem. Soc.*, 1946, **68**, 849) carried out a spectrophotometric study of bisdodecylaminocupric acetate, $Cu(OAc)_2,2C_{12}H_{25}{\cdot}NH_2$, and showed that a 0·04M-solution in chloroform, at room temperature, dissociated into dodecylamine and cupric acetate to the extent of 10%. Further evidence for the comparatively loose attachment of the amine is shown by the fact that an analogous disproportionation reaction to the one described above, but now involving the co-ordinately-bound groups, has been observed; *e.g.*,



$$(\mathrm{CuCl,C_{18}H_{37}{\cdot}NH_2})_4 + 4\mathrm{C_8H_{17}{\cdot}NH_3Cl}\ (+\ 2\mathrm{O}) \longrightarrow$$

$$4\left[\begin{matrix}\mathrm{Cl} & & \mathrm{NH_2{\cdot}C_8H_{17}}\\ & \mathrm{Cu} & \\ \mathrm{C_{18}H_{37}{\cdot}NH_2} & & \mathrm{Cl}\end{matrix}\right] (+\ 2\mathrm{H_2O}) \longrightarrow 2\mathrm{CuCl_2(C_{18}H_{37}{\cdot}NH_2)_2} + 2\mathrm{CuCl_2(C_8H_{17}{\cdot}NH_2)_2} \quad (\mathrm{D})$$

(IV.)

Small amounts of the intermediate compounds (I) and (IV) may be formed. These would disproportionate easily, however, and their separation and identification would be extremely difficult.

The ease of oxidation depends on (*a*) the halogen and (*b*) the basicity of the amine. The complexes of cuprous chloride with amines and with pyridine are more rapidly and more completely oxidised than those of the bromide. The effect of the amine is most clearly shown when the cuprous iodide amine complexes are considered. About 40% of cuprous iodide dodecylamine is oxidised in the presence of dodecylamine acetate, when equimolecular proportions of the reactants are heated together in solution for 2 hours (Reaction C; $X = I$, $Y = OAc$, $R = C_{12}H_{25}$). The corresponding reaction involving hexadecylamine takes place to the extent of only about 5%, even when the reactants are heated under reflux in solution for 4 or more hours.

The heating together of tetrakis(cuprous iodide octadecylamine) with octadecylamine acetate for several days, in high-boiling solvents, does not result in appreciable reaction.

Cupric iodide bisdodecylamine was obtained, pure, as a dark brown waxy solid. The complexes of cupric iodide with hexadecylamine and octadecylamine were dark brown powders, which could not be obtained free from the reactants, since they were formed in such small amounts.

EXPERIMENTAL.

I. *Oxidation Reactions of Tetrakis(cuprous chloride alkylamines).*—In this section, the reactions of the octadecylamine complex are described as typical for all the other members of the series.

(*a*) *In the presence of octadecylamine hydrochloride* (*Reaction* A; $X = Cl$, $R = C_{18}H_{37}$). Freshly prepared cuprous complex (0·75 g., 1 mol.) was dissolved in 30 ml. of hot chloroform and added to octadecylamine hydrochloride (0·63 g., 1·05 mols.) dissolved in 20 ml. of hot chloroform. The hot green solution changed to blue almost immediately, and was heated under reflux for ½ hour. The solution was cooled and filtered at 45°. The solid deposited was recrystallised three times from chloroform. A blue powder, m. p. 125°, was obtained (Found: Cl, 10·6; Cu, 9·4. Calc. for $C_{36}H_{78}N_2Cl_2Cu$: Cl, 10·6; Cu, 9·4%). The reaction involving dodecylamine was carried out in a similar manner, and a blue solid was isolated, m. p. 124° (Found: Cl, 14·1; Cu, 12·6. Calc. for $C_{24}H_{54}N_2Cl_2Cu$: Cl, 14·05; Cu, 12·6%).

(*b*) *In the presence of octadecylamine acetate* (*Reaction* C; $X = Cl$, $Y = OAc$, $R = C_{18}H_{37}$). Cuprous chloride mono-octadecylamine (1·5 g., 1 mol.) was treated with octadecylamine acetate (1·08 g., 0·9 mol.) in 100 ml. of benzene. The green solution, quickly changed to a deep blue colour, and was heated under reflux for 45 minutes and then cooled. A solid separated and was filtered off at about 35°; this was dark lilac-blue [fraction (i)]. The filtrate was dark blue and, when left overnight, deposited a lilac solid [fraction (ii)]. Fraction (i) was dissolved in 100 ml. of boiling benzene and cooled to 45°, at which temperature the solid was filtered off. It was recrystallised from 80 ml. of hot chloroform, giving a pale blue solid, m. p. 125° (Found: C, 64·8; H, 11·7; N, 4·3; Cl 10·6; Cu, 9·4. Calc. for $C_{36}H_{78}N_2Cl_2Cu$: C, 64·2; H, 11·7; N, 4·2; Cl, 10·6; Cu, 9·4%). Fraction (ii) was dissolved in 30 ml. of hot benzene and cooled. At about 45°, a solid separated which was filtered off at about 40°. Recrystallisation was repeated from 30 ml. of benzene. A lilac solid was obtained, m. p. 95° (Found: Cu, 8·8. Calc. for $C_{40}H_{34}N_2O_4Cu$: Cu, 8·8%). The reaction involving dodecylamine was carried out in a similar manner and two solids were obtained: blue, m. p. 124° (Found: Cl, 14·0; Cu, 12·5%), and lilac, transparent rectangular plates, m. p. 78° (Found: Cu, 11·1. Calc. for $C_{28}H_{60}O_4N_2Cu$: Cu, 11·5%). The reactions were also carried out in chloroform and in *n*-hexane with similar results.

(*c*) *In the presence of octylamine hydrochloride* (*Reaction* D). The cuprous complex (1·2 g., 1·0 mol.) was dissolved in 60 ml. of hot benzene and added to octylamine hydrochloride (0·43 g., 0·9 mol.) dissolved in 30 ml. of hot benzene. The hot green solution formed was heated under reflux for 45 minutes. It was then cooled; a solid separated at room temperature. This was filtered off and a light blue solid was obtained [fraction (i)] together with a green filtrate, which when left overnight deposited more blue solid [fraction (ii)]. Fraction (i) was recrystallised twice from 70 ml. of chloroform, the solid separating at about 45° being filtered off at 35° (Found: Cu, 9·1. Calc. for $C_{36}H_{78}N_2Cl_2Cu$: Cu, 9·4%). Fraction (ii) was not further treated (Found: Cu, 12·6. Calc. for $C_{16}H_{38}N_2Cl_2Cu$: Cu, 16·2%). Fraction (ii) appears to be a mixture of the two complexes of cupric chloride with octylamine and with octadecylamine; there is no doubt, however, that disproportionation occurs.

(*d*) *Oxidation of monopyridinocuprous chloride in the presence of pyridine hydrochloride* (*Reaction* B; $X = Cl$). Pyridinocuprous chloride (as prepared in Part II) was separated from the supernatant green liquid by decantation and dissolved in benzene (green solution). An excess (1·2 mols.) of pyridine hydrochloride dissolved in hot chloroform was added. The resulting dark solution quickly deposited a blue solid in large amounts. This was heated under reflux for a few minutes (the blue solid remaining insoluble) and then cooled. A light-blue micro-crystalline powder was filtered off. This was recrystallised from methyl alcohol, and fine pale blue needles were obtained (Found: Cl, 24·2; Cu, 21·9. Calc. for $C_{10}H_{10}N_2Cl_2Cu$: Cl, 24·2; Cu, 21·7%).

II. *Oxidation Reactions of Tetrakis(cuprous bromide alkylamines).*—The reactions of the octadecylamine complex are described as typical of those of all the cuprous bromide–amine complexes.

(*a*) *In the presence of octadecylamine hydrobromide* (*Reaction* A; $X = Br$, $R = C_{18}H_{37}$). Freshly prepared tetrakis(cuprous bromide octadecylamine) (1·0 g., 1 mol.) was dissolved in 25 ml. of warm benzene, and to it was added octadecylamine hydrobromide (0·85 g., 1 mol.) dissolved in 35 ml. of hot benzene. The resulting dark green solution was heated under reflux for about ½ hour, and then cooled to room temperature. A green solid was deposited, and the dark greenish-brown filtrate when left overnight deposited a further amount of green solid. This was separated and recrystallised from 60 ml. of benzene. A solid separated on cooling, and was filtered off, washed with cold benzene, and dried. A light green solid, m. p. 114°, was obtained (Found : C, 57·2; H, 10·2; N, 4·0; Br, 21·1. Calc. for $C_{36}H_{78}N_2Br_2Cu$: C, 56·6; H, 10·3; N, 3·7; Br, 21·0%).

(*b*) *In the presence of octadecylamine hydrochloride* (*Reaction* C; $X = Br$, $Y = Cl$, $R = C_{18}H_{37}$). Tetrakis(cuprous bromide octadecylamine) (1·0 g., 1 mol.) was dissolved in 25 ml. of hot benzene, and octadecylamine hydrochloride (0·74 g., 1 mol.), dissolved in 35 ml. of benzene, was added. The dark green solution was heated under reflux for about 45 minutes, and then cooled. An apple-green solid separated and was filtered off. The dark green filtrate deposited more green solid when kept. The apple-green solid dissolved in 80 ml. of chloroform to give a dark green solution, which on cooling re-deposited solid, which was filtered off. This had a different shade of green colour, and if it was recrystallised a further three times from 50 ml., 30 ml., and 20 ml. of chloroform, respectively, a blue solid was obtained, m. p. 125° (Found: Cu, 9·4%). The filtrate deposited a green solid on each occasion, m. p. 113° (Found : Br, 21·3%).

(*c*) *In the presence of octadecylamine acetate* (*Reaction* C; $X = Br$, $Y = OAc$, $R = C_{18}H_{37}$). Tetrakis-(cuprous bromide octadecylamine) (1·0 g., 1 mol.) and octadecylamine acetate (0·82 g., 1·02 mols.), dissolved in 25 ml. and 30 ml. of hot benzene, respectively, were heated together under reflux for about 2 hours. The hot green-blue solution on cooling deposited first a green solid and then a small amount of lilac solid. The blue-green filtrate, on further storage, deposited more lilac solid. The green solid, recrystallised from benzene, had m. p. 113° (Found : Br, 21·0. Calc. for $C_{36}H_{78}N_2Br_2Cu$: Br, 21·0%). The lilac solid, recrystallised twice from small quantities of benzene (20 ml.), had m. p. 95° (Found : Cu, 8·8%).

(*d*) *Oxidation of monopyridinocuprous bromide in the presence of pyridine hydrobromide* (*Reaction* B; $X = Br$). Pure pyridinocuprous bromide (0·1 g., 1 mol.), suspended in benzene, was treated with a solution of pyridine hydrobromide (0·07 g., 1 mol.) in 15 ml. of benzene–alcohol. Most of the complex dissolved and on being heated under reflux for a short time, a deep-brown solution was formed, together with an insoluble green solid. The brown solution, on cooling, deposited more green solid, m. p. 142°. This solid gave, with excess of pyridine, hexapyridinocupric bromide, $CuBr_2,6C_5H_5N$, and with hydrobromic acid, reddish-black pyridinium cupribromide $(C_5H_6N)_2CuBr_4$ (Pfeiffer and Pimmer, *loc. cit.*).

III. *Oxidation Reactions of Tetrakis*(*cuprous iodide alkylamines*).—(*a*) *Attempted reaction between tetrakis*(*cuprous iodide octadecylamine*) *and octadecylamine acetate* (*Reaction* C; $X = I$, $Y = OAc$, $R = C_{18}H_{37}$). A suspension of the cuprous iodide complex (0·5 g., 1 mol.) in 40 ml. of light petroleum (b. p. 80—100°) dissolved when octadecylamine acetate (0·36 g., 1 mol.) was added. The light-green solution was heated under reflux for several days (*a*) alone and (*b*) in the presence of excess of octadecylamine (to make the reaction conditions similar to those used in the dodecylamine work). The red solution finally obtained, on cooling, deposited first a white solid, m. p. 80—81° (m. p. of octadecylamine acetate 84°), and then unchanged cuprous complex.

(*b*) *Reaction between tetrakis*(*cuprous iodide hexadecylamine*) *and hexadecylamine acetate* (*Reaction* C; $X = I$, $Y = OAc$, $R = C_{16}H_{33}$). A solution of cuprous iodide monohexadecylamine (0·6 g., 1 mol.) in 30 ml. of light petroleum, containing a small amount of hexadecylamine, was heated under reflux with a solution of hexadecylamine acetate (0·4 g., 1·05 mols.) in 20 ml. of light petroleum. The initial green solution slowly became brown; after about 3 hours the solution was cooled, and a small amount of solid separated. This was filtered off, and a lilac solid was obtained; the brown filtrate on cooling continued to deposit a light-brown solid (a mixture of unchanged reactants and small amounts of the cupric iodide complex). When about 5—10 ml. of solution were left, no further solid separated and the brown solution on complete evaporation left a dark brown viscous solid, which on cooling in the refrigerator solidified and could be crushed to a brown powder, which however was not obtained pure.

(*c*) *Reaction between cuprous iodide dodecylamine and dodecylamine acetate* (*Reaction* C; $X = I$, $Y = OAc$, $R = C_{12}H_{25}$). Cuprous iodide (0·5 g., 1 mol.) was treated with dodecylamine (0·75 g., 1·4 mols.) in 40 ml. of light petroleum. After about 15 minutes, all the cuprous iodide had dissolved and a red solution was formed. To this hot solution, dodecylamine acetate (0·66 g., 1 mol.), dissolved in 30 ml. of light petroleum, was added, and the pale green solution formed was heated under reflux for 20 minutes. On cooling, this solution became dark green, but no solid was deposited. However, when it was left in an open dish for about 20 minutes, some solid was deposited. This was filtered off and a brown-lilac solid [fraction (i)] was obtained together with a green filtrate. This filtrate, on further storage, deposited more solid (lilac-brown, smelling strongly of free iodine) together with a dark brown filtrate which deposited no more solid, but left a dark brown, almost black, waxy solid [fraction (ii)] on complete evaporation. Passage of carbon dioxide through the dark brown light-petroleum solution precipitated, as the carbonate any excess of amine remaining in solution at this stage. The limited solubility of the cupric acetate amine complex and the extreme solubility of the cupric iodide amine complex thus makes a very effective separation possible. Fraction (i) was dissolved in 30 ml. of hot benzene, and the blue solution kept for an hour in an open beaker, whereupon a crystalline solid was deposited. This was filtered off, washed, and dried, transparent, lilac, rectangular plates being obtained (Found : Cu, 11·1%). Fraction (ii), *cupric iodide bisdodecylamine*, was extremely soluble in organic solvents (Found : Cu, 9·3. $C_{24}H_{54}N_2I_2Cu$ requires Cu, 9·25%).

(*d*) *Reaction between cuprous iodide dodecylamine and dodecylamine hydriodide* (*Reaction* A; $X = I$, $R = C_{12}H_{25}$). Cuprous iodide–dodecylamine, in benzene solution (1·0 g., 1 mol.) (see preceding paragraph), was treated with dodecylamine hydriodide (0·8 g., 0·97 mol.) in 20 ml. of benzene, and the solution heated under reflux for 5 hours. The light-brown solution obtained, on cooling, became dark red, and finally brown-red. The solution was transferred to an evaporating dish and kept overnight; a dark brown, waxy solid, very similar to that obtained as described in paragraph (*c*), remained. The solution of the solid, in light petroleum, was cooled in a freezing mixture; some solid separated (dodecylamine hydriodide ?) and was filtered off. Carbon dioxide was passed through the filtrate, and once more the solid was filtered off. The filtrate was evaporated to dryness. Analysis of the waxy residue indicated that it was the cupric iodide complex contaminated with unchanged dodecylamine hydriodide and probably some iodine (Found: I, 43·5; Cu, 7·25. Calc. for $C_{24}H_{54}N_2I_2Cu$: I, 36·9; Cu, 9·25%).

Messrs. Weiler and Strauss, Oxford, carried out the microanalyses. Our thanks are due to Armour & Co. Ltd., for certain samples of amines, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. G. W.).

UNIVERSITY COLLEGE, SOUTHAMPTON.

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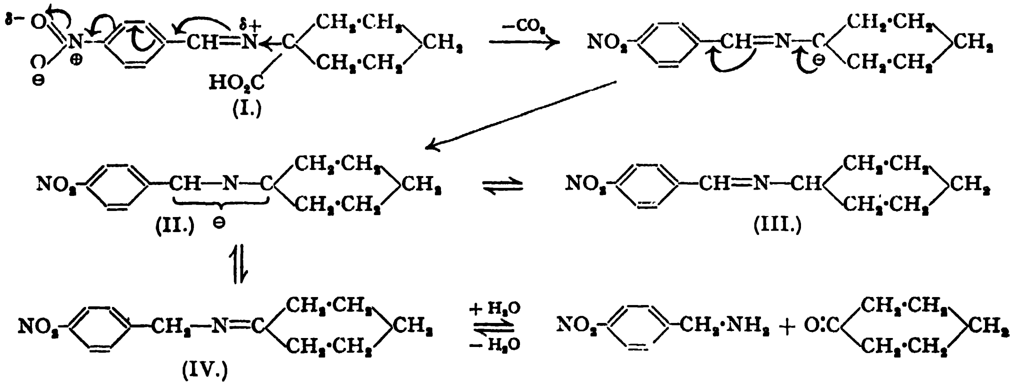
29. *Triad Prototropic Systems. Part I. The Mobility of the Azomethine System during Decarboxylation.*

By FAWZY G. BADDAR.

Whereas *p*-nitrobenzylidene-ethylamine and -cyclo*hexylamine*, and *o*-chlorobenzylidene-*cyclo*hexylamine and -ethylamine do not undergo tautomerism when refluxed with 50% glycerol or even dry pyridine, 1-amino*cyclo*hexane-1-carboxylic acid and alanine are readily degraded, when heated with *p*-nitro- or *o*-chloro-benzaldehyde in 75% pyridine, to *cyclo*hexanone and acetaldehyde, respectively. This shows that the anion (cf. II and VI) resulting from the decarboxylation of the corresponding azomethine-carboxylic acid (cf. I and V), which is supposed to be formed as an intermediate product, is more mobile than the corresponding azomethine (cf. III and VII). Further, *m*-chlorobenzaldehyde and dichloroacetone degrade alanine and α-amino*iso*butyric acid to acetaldehyde and acetone, respectively. In all cases the degradation is facilitated by replacing 50% glycerol by 75% pyridine.

IN a previous publication (Baddar, *J.*, 1949, S 163), the degradation of α-amino-acids by certain carbonyl compounds was interpreted electronically. According to this interpretation the degradation can be effected by any carbonyl compound, in which the carbonyl group is preferably directly attached to, or conjugated with, strong electron-attracting groups. The azomethine systems are known to be immobile (cf. Ingold and Piggott, *J.*, 1922, **121**, 2381) and tautomerism in these systems requires strong nucleophilic reagents such as sodium ethoxide (cf. Ingold, Shoppee, and Thorpe, *J.*, 1926, 1477; Ingold and Shoppee, *J.*, 1929, 1199). The degradation of α-amino-acids with certain carbonyl compounds is supposed to take place by the condensation of the carbonyl compound with the α-amino-acid to give an azomethine-carboxylic acid (cf. I), which is then decarboxylated to an intermediate anion (cf. II). This, owing to its mobility, can combine with a free proton to give a mixture of the two possible tautomerides (cf. III and IV).

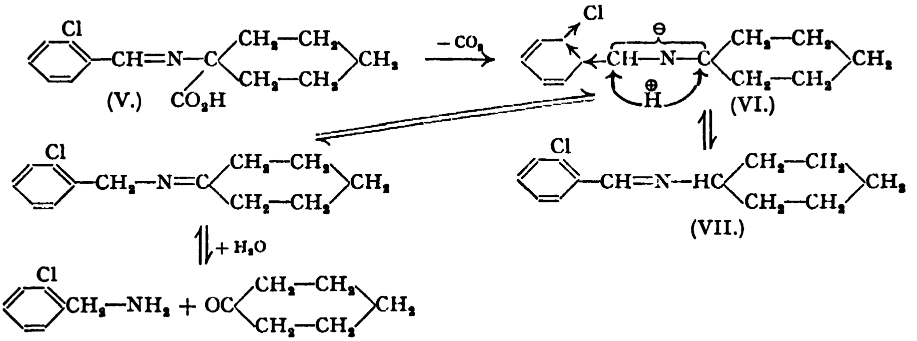


In the present investigation the author made a comparative study of the effect of decarboxylation on the mobility of these systems. It was found that, whereas certain azomethines are immobile even in presence of strong nucleophilic reagents such as sodium ethoxide, the system becomes mobile, even in presence of a weak nucleophilic reagent such as pyridine, if decarboxylation is expected to take place as an intermediate step. Thus, whereas, *p*-nitrobenzylidene-ethylamine, and -*cyclo*hexylamine (III) gave practically no acetaldehyde or *cyclo*hexanone respectively when refluxed with 50% glycerol or even with dry pyridine, alanine (cf. Baddar, *loc. cit.*) and 1-amino*cyclo*hexane-1-carboxylic acid gave, when refluxed with 50% glycerol, acetaldehyde, and *cyclo*hexanone respectively.

Similarly, whereas *o*-chlorobenzylidene-*cyclo*hexylamine (VII) and -ethylamine did not undergo tautomerism when refluxed with dry pyridine or, in the case of the former compound, with alcoholic sodium ethoxide, 1-amino*cyclo*hexane-1-carboxylic acid and alanine were degraded with *o*-chlorobenzaldehyde, when heated with 75% pyridine, to *cyclo*hexanone and acetaldehyde respectively.

If the azomethine-carboxylic acids (I) and (V) are formed as intermediate products and the ionic nature of decarboxylation is accepted (cf. Brown and Hammick, *J.*, 1949, 173), the corresponding azomethine-carboxylate ions afford on decarboxylation the mesomeric azomethine anions (II) and (VI) respectively. This naturally requires much less energy than that necessary for the extraction of a proton from the azomethine systems (III) and (VII).

o-Nitrobenzaldehyde with 1-amino*cyclo*hexane-1-carboxylic acid gave an indigo-blue compound, but no *cyclo*hexanone was isolated. The nature of this compound, as well as those similarly obtained from alanine and α-amino*iso*butyric acid (cf. Baddar, *loc. cit.*), is under investigation. The yield of *cyclo*hexanone liberated from 1-amino*cyclo*hexane-1-carboxylic acid with *m*-nitrobenzaldehyde was much less than that with *p*-nitrobenzaldehyde. This supported the previous assumption by Baddar (*loc. cit.*) that in *m*-nitrobenzaldehyde the nitro-group operates only by its relatively weak inductive effect (—*I*), whereas, in *p*-nitrobenzaldehyde it operates by both its inductive (—*I*) and its strong tautomeric (—*T*) effect.



In *o*-chlorobenzaldehyde the chlorine atom appears to operate only by its strong inductive effect (—*I*), thus effecting the decarboxylation of the azomethine-carboxylic acid (V) and enhancing the mesomeric shift of electrons in the intermediate anion (VI). The electromeric effect (+*E*) of the chlorine atom appears not to operate in this degradation, as the yield of acetaldehyde and acetone liberated from alanine and α-amino*iso*butyric acid, respectively, by *o*-chlorobenzaldehyde was slightly higher than that liberated by *m*-chlorobenzaldehyde under the same conditions.

The above observations, however, add a further proof to the ionic nature of prototropy (cf. Ingold, Shoppee, and Thorpe, *loc. cit.*; Ingold and Shoppee, *loc. cit.*; Shoppee, *J.*, 1931, 1225).

The degradation of alanine and α-amino*iso*butyric acid to acetaldehyde and acetone respectively was effected also by *s*-dichloroacetone in boiling water. The yield increased when water was replaced by 50% glycerol. This showed that the effect of glycerol in increasing the yield is not merely to aid dissolution or wetting but is probably caused by its higher boiling point and its greater nucleophilic character. Under similar conditions *s*-dichloro*iso*propyl alcohol failed to effect this degradation. This showed that the carbonyl group in *s*-dichloroacetone is involved, probably by a mechanism similar to that mentioned above. In *s*-dichloroacetone the two chlorine atoms exert more electron-attraction on the system than the one chlorine atom in the chlorobenzaldehydes, and thus cause an easier degradation.

EXPERIMENTAL.

The degradation of α-amino-acids was carried out as mentioned by Baddar (*loc. cit.*). The liberated carbonyl compounds were identified as their 2 : 4-dinitrophenylhydrazones. Yields are reproducible within ±10%, although they are of no quantitative significance as the hydrazones were contaminated with traces of those of the original carbonyl compounds.

Degradation of Alanine with o- *and* m-*Chlorobenzaldehyde.*—(i) *o*-Chlorobenzaldehyde (0·46 g., 1 mol.) and alanine (0·3 g., 1 mol.) were heated on a boiling water-bath with 75% pyridine (20 c.c.) in a carbon dioxide atmosphere for 3 hours. The liberated acetaldehyde was precipitated as its 2 : 4-dinitrophenylhydrazone (*ca.* 0·09 g.) (Found: C, 43·2; H, 3·7; N, 24·8. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·0%), which was crystallised from alcohol and identified by its m. p. and mixed m. p. with an authentic specimen.

(ii) The experiment was repeated using *m*-chlorobenzaldehyde, and the liberated acetaldehyde was precipitated as its 2 : 4-dinitrophenylhydrazone (*ca.* 0·065 g.) and identified as above (Found : N, 25·4, 24·8%).

When the degradation was carried out with *o*-chlorobenzaldehyde (0·46 g.) in 50% glycerol (cf. Baddar, *loc. cit.*), only *ca.* 0·01 g. of acetaldehyde 2 : 4-dinitrophenylhydrazone was collected, which after two crystallisations were identified as above.

Degradation of Alanine with s-*Dichloroacetone.*—A mixture of dichloroacetone (0·84 g., 1 mol.), alanine (0·6 g.), and water (20 c.c.) was refluxed in a carbon dioxide atmosphere for 3 hours. The precipitated hydrazone (*ca.* 0·07 g.) was crystallised from dilute alcohol and identified as above (Found : C, 42·9; H, 3·6; N, 24·3%).

When water was replaced by 50% glycerol, the yield of acetadehyde enormously increased. Pyridine could not be used as it appeared to react with dichloroacetone.

α-Amino*iso*butyric acid, when similarly treated, gave acetone.

Under similar conditions *s*-dichloro*iso*propyl alcohol failed to effect the degradation of alanine.

*Degradation of α-Amino*iso*butyric Acid with* o- *and* m-*Chlorobenzaldehyde.*—A mixture of the chlorobenzaldehyde (0·46 g., 1 mol.), α-amino*iso*butyric acid (0·35 g., 1 mol.), and 75% pyridine (20 c.c.) was heated for 3 hours as above.

(i) With *o*-chlorobenzaldehyde, the precipitated derivative (*ca.* 0·1 g.) was crystallised from dilute alcohol and identified as acetone 2 : 4-dinitrophenylhydrazone (Found : C, 45·5, 45·3; H, 4·1, 4·3; N, 23·0. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2, N, 23·95%), by its m. p. and mixed m. p. with an authentic specimen.

(ii) With *m*-chlorobenzaldehyde, the precipitated acetone 2 : 4-dinitrophenylhydrazone (*ca.* 0·55 g.) was identified as above (Found : C, 45·8; H, 4·3; N, 23·5, 23·4%).

With 50% glycerol practically no acetone was liberated.

Degradation of 1-*Amino*cyclo*hexane*-1-*carboxylic Acid with* p- *and* m-*Nitrobenzaldehyde.*—The amino-acid (0·5 g., 1 mol.) and the nitrobenzaldehyde (0·5 g., 1 mol.) were heated with 50% glycerol (20 c.c.) for 3 hours in a carbon dioxide atmosphere. Water was added and the product distilled in a carbon dioxide atmosphere. The distillate was treated with a solution of 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated derivative was extracted with boiling alcohol, filtered from the insoluble derivative of the nitrobenzaldehyde, diluted with water, and allowed to crystallise. In case of *p*-nitrobenzaldehyde, the yield of the crystalline derivative was about 0·15 g., and was identified as *cyclo*hexanone 2 : 4-dinitrophenylhydrazone by m. p. and mixed m. p. (Found : C, 51·7, 52·0; H, 5·2, 5·0; N, 20·6, 20·1. Calc. for $C_{12}H_{14}O_4N_4$: C, 51·8; H, 5·0; N, 20·1%).

With *m*-nitrobenzaldehyde, traces of the *cyclo*hexanone derivative were isolated and were identified by m. p. and mixed m. p.

o-Nitrobenzaldehyde gave an indigo-blue compound but practically no *cyclo*hexanone came over on distillation (cf. Baddar, *loc. cit.*).

Degradation of 1-*Amino*cyclo*hexane*-1-*carboxylic Acid with* o-*Chlorobenzaldehyde.*—A mixture of *o*-chlorobenzaldehyde (0·3 g.), the α-amino-acid (0·3 g.), and 75% pyridine (20 c.c.) was treated as above. The reaction mixture was acidified with dilute hydrochloric acid and distilled. The distillate was treated with 2 : 4-dinitrophenylhydrazine hydrochloride, the precipitated derivative extracted with hot alcohol, and the solution filtered. The filtrate was diluted with water and allowed to crystallise. The product was recrystallised from dilute alcohol and identified by m. p. and mixed m. p. as *cyclo*hexanone 2 : 4-dinitrophenylhydrazone. The fraction insoluble in alcohol crystallised from acetic acid in orange-red crystals, m. p. 208·5—209·5°, undepressed on admixture with an authentic specimen of *o*-chlorobenzaldehyde 2 : 4-dinitrophenylhydrazone.

When the degradation was carried out in 50% glycerol instead of 75% pyridine, practically no *cyclo*hexanone was liberated.

o-*Chlorobenzylidene-ethylamine.*—*o*-Chlorobenzaldehyde (5·0 g.) was treated with anhydrous ethylamine (6 c.c.) in the cold. Heat was evolved and the aldehyde dissolved. The mixture was left overnight at room temperature, diluted with water, and extracted with ether. The o-*chlorobenzylidene-ethylamine* was dried (Na_2SO_4) and distilled, to give a colourless oil, b. p. 84·5°/3 mm. (Found : C, 64·4; H, 6·0; N, 8·0, 8·3; Cl, 21·4, 21·5. $C_9H_{10}NCl$ requires C, 64·5; H, 6·0; N, 8·4; Cl, 21·2%). It was soluble in dilute hydrochloric acid, and decomposed to give the original aldehyde on warming.

p-*Nitrobenzylidene*cyclo*hexylamine* (III).—An ethereal solution of *p*-nitrobenzaldehyde (1 g.) and *cyclo*hexylamine (0·66 g.) was set aside overnight. The ethereal solution was washed with 2% acetic acid and with sodium hydrogen carbonate solution, and then dried (Na_2SO_4). Evaporation of the ether left a *benzylidene* derivative (*ca.* 1·5 g.), which crystallised from light petroleum (b. p. 60—70°) in colourless prismatic needles, m. p. 85·5—86° (Found : C, 67·4, 66·9; H, 6·9, 6·9; N, 11·8, 12·2. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

o-*Chlorobenzylidene*cyclo*hexylamine* (VII).—An ethereal solution of *o*-chlorobenzaldehyde (2·8 g.) and *cyclo*hexylamine (2·0 g.) was treated as above. The dry product was distilled in a vacuum, to give o-*chlorobenzylidene*cyclo*hexylamine* as a colourless oil, b. p. 135—136°/3 mm. (*ca.* 3·8 g.) (Found : C, 70·0, 70·6; H, 7·0, 7·3; N, 6·4, 6·3; Cl, 16·5, 15·6. $C_{13}H_{16}NCl$ requires C, 70·4; H, 7·2; N, 6·3; Cl, 16·0%). It dissolved in dilute hydrochloric acid and decomposed on warming.

p-*Nitrobenzylidene-ethylamine.*—A mixture of *p*-nitrobenzaldehyde (0·5 g.) and 30% aqueous ethylamine (4 c.c.) was heated for few minutes on a water-bath. The mixture was diluted with water, and the precipitated *product* (0·55 g.) was filtered off and crystallised from light petroleum (b. p. 60—70°) in colourless silky needles, m. p. 76—77° (Found : C, 61·0, 60·7; H, 5·7, 5·4; N, 15·4, 15·5%; *M*, 176. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·6; N, 15·7%; *M*, 178).

Tautomerism of o-*Chlorobenzylidene-ethylamine.*—(i) When *o*-chlorobenzylidene-ethylamine (0·5 g.) was heated with 50% glycerol (20 c.c.) for 3 hours in a carbon dioxide atmosphere, practically no acetaldehyde was liberated. A similar result was obtained when glycerol was replaced by dry pyridine and the mixture refluxed for 6 hours, followed by acidification with dilute sulphuric acid and distillation in a carbon dioxide atmosphere.

(ii) The azomethine (0·5 g.) was refluxed with alcoholic sodium ethoxide (1 g. of sodium in 20 c.c. of absolute alcohol) for 5 hours. The solution was acidified with dilute sulphuric acid, and the liberated acetaldehyde was driven off by a stream of carbon dioxide. An appreciable amount of acetaldehyde 2 : 4-dinitrophenylhydrazone was collected and identified by its m. p. and mixed m. p. However, a similar result was obtained when the experiment was repeated with ethylamine itself.

Tautomerism of p-*Nitrobenzylidene-ethylamine and* -cyclo*hexylamine.*—The azomethines were refluxed with 50% glycerol or dry pyridine as stated above. The product was acidified with dilute sulphuric acid and distilled. Practically no acetaldehyde or *cyclo*hexanone was obtained.

Tautomerism of o-*Chlorobenzylidene*cyclo*hexylamine.*—The azomethine was similarly refluxed with 50% glycerol, dry pyridine or sodium ethoxide. The acidified solution was distilled, and the distillate treated with 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated derivative was extracted with hot alcohol, and the extract filtered, diluted with water, and allowed to crystallise. The precipitated product, *o*-chlorobenzaldehyde 2 : 4-dinitrophenylhydrazone (trace), melted at 200—202°.

M. p.s are not corrected. Microanalyses were carried out by Drs. Weiler and Strauss of Oxford.

FOUAD I UNIVERSITY, FACULTY OF SCIENCE, CAIRO, EGYPT. [*Received, September 17th,* 1949.]

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30. *Colchicine and Related Compounds. Part IX.*

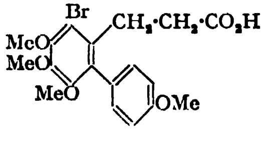
By J. W. COOK, G. T. DICKSON, J. JACK, J. D. LOUDON, J. MCKEOWN, J. MACMILLAN, and W. F. WILLIAMSON.

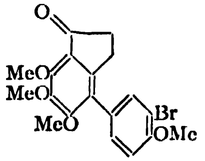
In Part V (*J.*, 1945, 176) it was shown that a degradation product of colchicine, deaminocolchinol methyl ether, is a derivative of dibenz*cyclo*heptatriene, and a synthesis of this parent hydrocarbon was described in Part VI (*J.*, 1947, 746). The present communication records the preparation and cyclisation of *β-2-diphenylylpropionic acid* (III) and some of its derivatives with a view to determine whether this type of method is adaptable to the synthesis of dibenz*cyclo*heptadiene derivatives related to colchicine. In agreement with the conclusions of von Braun and his collaborators, the main product of cyclisation of (III) was found to be *4-phenylindanone* (IV), but there was also formed, albeit in yields of less than 10%, the seven-membered ring ketone (V). The cyclisation of various methoxylated derivatives of (III) was also examined, but in no other case was evidence of seven-membered ring formation obtained. The ketone (V) was also synthesised from diphenic acid. Poor yields at an early stage discouraged attempts to extend the method to the synthesis of derivatives of (V).

Observations are recorded on the desulphuration of thiol esters of some aromatic acids by means of Raney nickel.

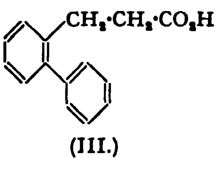
THE course, (I) ⟶ (II), taken by the Friedel–Crafts reaction when applied to the acid chloride of (I) (Barton, Cook, and Loudon, Part VIII, *J.*, 1949, 1079; Huang, Tarbell, and Arnstein, *J. Amer. Chem. Soc.*, 1948, **70**, 4181) is probably determined by a combination of orienting influences and steric factors. Considered from the point of view of cyclisation to a 7-membered ring, the methoxylation pattern is unfavourable : in particular, the position of the methoxyl group in the disubstituted nucleus is unfortunate, since the directive powers of the substituent are not enlisted to offset the steric difficulty which is implicit in the rule that, *ceteris paribus*, a 5-membered ring is formed in preference to a 7-membered ring. Because of the importance of dibenz*cyclo*heptadienones in the chemistry of colchicine we have now investigated the direction of ring-closure in several compounds related to (I).

(I.)

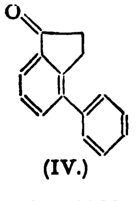




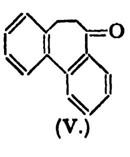
(II.)



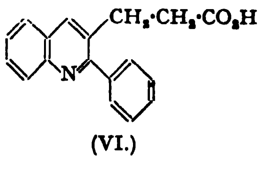
(III.)



(IV.)



(V.)

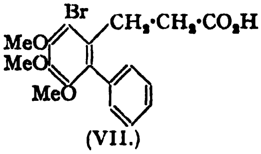


(VI.)

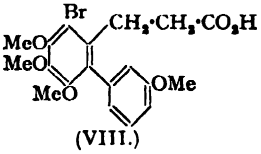
Von Braun and Manz (*Annalen*, 1929, **468**, 258) have reported that the indanone (IV) is the sole product of cyclising (III) by the Friedel–Crafts reaction. Their conclusion, however, is based on very unconvincing evidence : the indanone (IV) is described as an oil, alleged to be homogeneous because it afforded a sharp-melting semicarbazone (no analyses are given), and identified only through oxidation with nitric acid which appeared to yield a nitrated derivative of phthalic acid as judged from a qualitative nitrogen test and a fluorescein reaction. For re-investigation, diphenyl-2-aldehyde was conveniently prepared from the acid by the McFadyen–Stevens process (*J.*, 1936, 584) and was condensed with malonic acid to β-2-diphenylylacrylic acid (cf. Zaheer and Faseeh, *J. Indian Chem. Soc.*, 1944, **21**, 381). Hydrogenation of the latter acid using a palladium catalyst gave the required β-2-*diphenylylpropionic acid* (III) which, however, was markedly different from the compound described by von Braun *et al.* Repetition of the method of preparation used by these authors, and based on the condensation of 2-bromomethyldiphenyl (here obtained by an alternative method) with ethyl sodiomalonate, showed that the properties which they ascribe to (III) correspond with the properties now found for (2-*diphenylylmethyl*)*malonic acid.* The latter acid, when heated, afforded a sample of (III) which was identical with the material produced by our first method of preparation.

Cyclisation of (III) by the Friedel–Crafts reaction gave a crystalline solid as main product, together with some oil. The solid was identified as 4-*phenylindanone* (IV) by oxidation with potassium permanganate to 3-phenylphthalic acid and conversion of the latter into fluorenone-1-carboxylic acid of which an authentic specimen was available. A portion of the oil was oxidised with sodium dichromate in acetic acid, and the formation of phenanthraquinone and of diphenic acid clearly indicated the presence of some dibenz*cyclo*heptadienone (V) (cf. Part VI, Cook, Dickson, and Loudon, *J.*, 1947, 746). This was confirmed when the remainder of the oil was treated with 2 : 4-dinitrophenylhydrazine and, from the resulting mixture, the 2 : 4-dinitrophenylhydrazone of (V) was isolated. The total quantity of (V) in the cyclisation product was small—less than 10%.

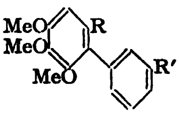
As an alternative to the Friedel–Crafts type of cyclisation, the action of anhydrous hydrogen fluoride on the acids (I) and (III) was examined. By this means (III) was again converted into a mixture of (IV) and (V), the presence of the latter being inferred from the isolation of phenanthraquinone following oxidation. Frank, Fanta, and Tarbell (*J. Amer. Chem. Soc.*, 1948, **70**, 2314) state that (I) does not undergo cyclisation when treated with hydrogen fluoride, but we now find that it affords a mixture of (II) and the debrominated indanone (II; H for Br), apparently formed by displacement and either migration or elimination of the bromo-substituent. Accordingly, in the respective cases, the Friedel–Crafts and the hydrogen fluoride method of cyclisation appear to produce essentially similar results and, when applied to (I), the latter method has the advantages of giving more easily separable products in better total yield (cf. Part VIII, *loc. cit.*). The production of (V) from (III) encourages the hope that dibenz*cyclo*heptadienones may be synthesised by this method when favourable orienting influences are present, but it is relevant to add that Borsche and Sinn (*Annalen*, 1939, **538**, 283) were unable to obtain the 7-membered cyclic ketone by cyclisation of (VI) although in this case a 5-membered ring was not formed.



(VII.)



(VIII.)



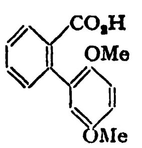
(IX; R = CO$_2$H, R′ = H.)
(XI; R = CHO, R′ = H.)
(XIII; R = CH:CH·CO$_2$H, R′ = H.)
(XV; R = CH$_2$·CH$_2$·CO$_2$H, R′ = H.)

(X; R = CO$_2$H, R′ = OMe.)
(XII; R = CHO, R′ = OMe.)
(XIV; R = CH:CH·CO$_2$H, R′ = OMe.)
(XVI; R = CH$_2$·CH$_2$·CO$_2$H, R′ = OMe.)

In order to ascertain whether the position of the methoxyl group in the disubstituted nucleus materially affects the course of the reaction (I) ⟶ (II), the two *acids* (VII) and (VIII) were synthesised and examined. The syntheses followed the lines already described for (I) (Part VIII, *loc. cit.*) and involved condensations of 1-phenyl- and 1-m-*methoxyphenyl*-3 : 3-*dimethyltriazen* with methyl 3 : 4 : 5-trimethoxybenzoate to form the *methyl* esters of the *acids* (IX) and (X) respectively (for by-products, cf. Experimental). Cyclisation of these acids by warming with thionyl chloride yielded *fluorenone* derivatives, a pair of isomers which were not individually oriented being obtained from the acid (X). Reduction of (IX) and (X) to the respective *aldehydes* (XI and XII) and subsequent conversion into the acrylic (XIII and XIV) and propionic *acids* (XV and XVI) were effected by standard methods. Bromination of (XV) and (XVI) gave the *bromo-acids* (VII) and (VIII), respectively. On cyclisation with hydrogen fluoride each of the acids (XV) and (XVI) gave a corresponding *indanone* derivative, and the failure of the cyclisation products to furnish (coloured) phenanthraquinones in the oxidation test indicated the absence of dibenz*cyclo*heptadienones. The same test was again negative when applied to the cyclisation products of the bromo-acids (VII) and (VIII). The former acid, when cyclised by either the Friedel–Crafts or the hydrogen fluoride method, gave only gummy products which were probably mixtures. On the other hand, (VIII) was cyclised by hydrogen fluoride to a brominated ***indanone*** which, on debromination, afforded 5 : 6 : *7-trimethoxy-*4-m-*methoxyphenyl-indan-*1-*one*, already obtained by direct cyclisation of (XVI). Accordingly, it may be concluded that, in this case at least, cyclisation is achieved by displacement and migration of bromine, and that in neither case is there any significant tendency to form a 7-membered ring.

It is noteworthy that the displacement and migration of bromine, encountered in these cyclisations to indanone derivatives, finds its counterpart in the isomerisation which accompanies cyclisation of β-(9-*s*-octahydroanthranyl)propionic acid to 1′-keto-9 : 10-*cyclo*penteno-*s*-octahydrophenanthrene (Badger, Carruthers, Cook, and Schoental, *J.*, 1949, 169). In the latter case it is a saturated carbon chain which migrates, and in both types hydrogen fluoride is an effective agent.

2′ : 5′-Dimethoxydiphenyl-2-carboxylic acid (XVII), prepared through the *methyl* ester by condensing 1-(*o*-carbomethoxyphenyl)-3 : 3-dimethyltriazen and 1 : 4-dimethoxybenzene, was next examined in the hope of applying the synthetic procedure to a case favourable to 7-membered ring formation. The project, however, failed since the ester was recovered unchanged from all attempts to convert it by reaction with hydrazine hydrate into the hydrazide. Moreover, even mild treatment of (XVII) with thionyl chloride yielded the *lactone* (XVIII) of 2′-hydroxy-5′-methoxydiphenyl-2-carboxylic acid.



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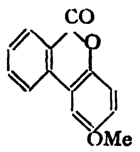
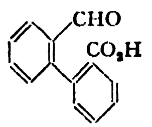
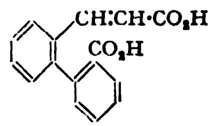


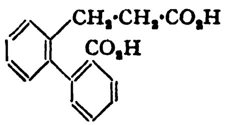
(XVIII.)



(XIX.)



(XX.)



(XXI.)

A different approach to the synthesis of the unsubstituted ketone (V) was made starting from diphenic anhydride. This reacted with hydrazine hydrate to form the half hydrazide of diphenic acid, which with benzenesulphonyl chloride afforded the N-*benzenesulphonyl* derivative. The latter was also obtained by the direct action of benzenesulphonhydrazide on diphenic anhydride and by an adaptation of the McFadyen–Stevens process gave the *aldehydo-acid* (XIX) in rather poor yield. Condensation of (XIX) with malonic acid yielded an unsaturated dibasic acid (XX) which was hydrogenated by use of a palladium catalyst to the corresponding saturated acid (XXI). From this acid by heating (*a*) the barium salt alone or (*b*) the sodium salt with acetic anhydride there was obtained in each case a gum which afforded the 2 : 4-dinitrophenylhydrazone of (V). The method, however, is inferior to the synthesis of (V) recently reported by Rapoport and Williams (*J. Amer. Chem. Soc.*, 1949, 61, 1774) who prepared the same acid (XXI) in several stages from phenanthraquinone mono-oxime and achieved a more satisfactory cyclisation through the corresponding dinitrile by means of Ziegler's procedure.

In course of the foregoing synthetic work the frequent need of reducing a carboxylic acid to the corresponding aldehyde prompted some investigation of reductive desulphuration of thiolcarboxylic esters by means of Raney nickel. Wolfrom and Karabinos (*J. Amer. Chem. Soc.*, 1946, 68, 1455) report the formation of aldehydes in this way, whilst Prelog *et al.* (*Helv. Chim. Acta*, 1946, 29, 684) recommend the process for the preparation of primary alcohols. The results of our experiments show the prevalence of reduction beyond the aldehyde stage as well as the incidence of side reactions, but the activity of the catalyst may well be the critical factor determining the nature of the product (cf. Spero, McIntosh, and Levin, *J. Amer. Chem. Soc.*, 1948, 70, 1907) and requires further inquiry. Previous workers have confined their attention to thiol esters derived from methane-, ethane-, or toluene-ω-thiol, but it seems probable that in many cases these malodorous thiols may be replaced by thiophenols such as thio-*p*-cresol which was mainly used in the present connection.

By use of Raney nickel as prepared by Mozingo (*J. Amer. Chem. Soc.*, 1943, 65, 1015) the half *thiol-ester* from diphenic anhydride and thio-*p*-cresol was converted into 2′-hydroxymethyldiphenyl-2-carboxylic acid, and p-*tolyl* o-*carbomethoxythiolbenzoate* [o-$C_6H_4(CO_2Me)\cdot CO\cdot S\cdot C_7H_7$] yielded phthalide. A test experiment on *p*-tolyl thiolbenzoate showed the formation of benzaldehyde (*ca.* 10%) and benzyl alcohol (23%); moreover, examination of the more volatile products from ethyl thiolbenzoate revealed unexpectedly the presence of much benzene. Both *ethyl* and p-*tolyl* 3 : 4 : 5-*trimethoxythiolbenzoate* afforded 3 : 4 : 5-trimethoxybenzyl alcohol (40%) together with 1 : 2 : 3-trimethoxybenzene (20—30%) and the formation of these products was largely independent of the conditions or of the thiol-ester used. The results, therefore, show that scission of the original carboxyl group may accompany desulphuration and reduction, and it may be recalled that similar competitive processes have been noted in connection with the Rosenmund reduction of acid chlorides (Späth, *Monatsh.*, 1919, **40**, 129; Rosenmund, Zetzsche, and Heise, *Ber.*, 1921, **54**, 638) where again the activity of the catalyst is of paramount importance.

EXPERIMENTAL.

Diphenyl-2-aldehyde from the 2-Carboxylic Acid.—Methyl diphenyl-2-carboxylate (14·8 g.), heated under reflux with hydrazine hydrate (98%; 25 g.) and ethanol (30 c.c.) for 5 hours, afforded the *hydrazide*, as colourless needles, m. p. 136·5°, from methanol (Found: C, 73·8; H, 5·6. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7%). The product (9·6 g.) in pyridine (40 c.c.) was treated at 0° with benzenesulphonyl chloride (8·2 g.) and the whole was left for 3 hours at room temperature before it was added to a mixture of ice and hydrochloric acid. The resulting *benzenesulphonhydrazide* of diphenyl-2-carboxylic acid formed colourless needles, m. p. 173·5°, from methanol (Found: C, 64·8; H, 4·6. $C_{19}H_{16}O_3N_2S$ requires C, 64·8; H, 4·6%). A solution of the above sulphonhydrazide (14·3 g.) in ethylene glycol (70 c.c.) was treated at 160° with anhydrous sodium carbonate (21 g.) and after 80 seconds the reaction was quenched by pouring the mixture into hot water. The required aldehyde, recovered in ether, had b. p. 162°/12 mm.; the yield was 55%, based on the acid.

1-o-*Tolyl*-3 : 3-*dimethyltriazen.*—*o*-Toluidine (32·1 g.) in concentrated hydrochloric acid (108 c.c.) and water (72 c.c.) was diazotised at 0° with a concentrated aqueous solution of sodium nitrite (21 g.) and the resulting solution was added with stirring to an ice-cold solution of dimethylamine (33%; 48 g.) in 30% aqueous sodium carbonate (300 c.c.). The required *triazen*, b. p. 128—129°/12 mm., was recovered from a dried and washed benzene extract (Found: C, 66·1; H, 7·8. $C_9H_{13}N_3$ requires C, 66·3; H, 8·0%).

2-Methyldiphenyl was obtained in poor yield by the following procedure: Glacial acetic acid (40 c.c.) was gradually added to a boiling solution of the above triazen (45 g.) in benzene (400 c.c.) and the whole was heated under reflux for 16 hours. The resulting solution was washed in turn with water, dilute hydrochloric acid, dilute alkali, and again with water. Fractionation of the dried benzene solution gave 2-methyldiphenyl, b. p. 128—130°/15 mm. (9%), and neutralisation of the acid washings gave indazole (21%), m. p. 144—145° (Found: C, 71·5; H, 5·0; N, 23·8. Calc. for $C_7H_6N_2$: C, 71·2; H, 5·1; N, 23·7%).

2-Bromomethyldiphenyl was prepared in 65% yield by adding (2 hours) a solution of bromine (4·1 g.) in carbon tetrachloride (12 c.c.) to a strongly irradiated, boiling solution of 2-methyldiphenyl (4·1 g.) in the same solvent (25 c.c.) which contained a trace of iodine and was covered with a layer of water (6 c.c.). After further heating (½ hour), the cooled solution was washed in turn with sulphurous acid, dilute sodium carbonate, and water before being dried and concentrated. The required product distilled at 168—172°/11 mm. (von Braun and Manz record b. p. 166°/12 mm.).

(2-*Diphenylylmethyl*)*malonic Acid.*—The corresponding diethyl ester, prepared as described by von Braun and Manz (*loc. cit.*), was hydrolysed by potassium hydroxide in boiling ethanol–water. After distillation of the ethanol and extraction of the diluted solution with ether, the aqueous residue was acidified and the precipitated oil was extracted with much boiling water from which the *acid* slowly crystallised, having m. p. 125·5—127·5° (decomp.); it was dried at 65° *in vacuo* (Found: C, 71·1; H, 5·1. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

β-2-*Diphenylylpropionic Acid* (III).—(*a*) β-2-Diphenylylacrylic, m. p. 196°, prepared essentially as described by Zaheer and Faseeh (*loc. cit.*) who give m. p. 202°, was dissolved (6·2 g.) in glacial acetic acid (450 c.c.) and was hydrogenated using palladium-black as catalyst (0·3 g.) at ordinary temperature and pressure. Absorption was complete in 2½ hours and the product, recovered from the solvent, had m. p. 110—113°. Methylation with diazomethane in ether gave the *methyl* ester, b. p. 181·5—182°/10 mm. (Found: C, 80·1; H, 6·5. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%), from which the *acid* was recovered by hydrolysis and formed plates, m. p. 112·5—113°, from aqueous acetic acid (Found: C, 79·8; H, 6·0. $C_{15}H_{14}O_2$ requires C, 79·7; H, 6·2%). (*b*) The same acid, m. p. and mixed m. p. 111—113°, was obtained when 2-diphenylylmethylmalonic acid was heated at 130° until evolution of carbon dioxide ceased and the product was crystallised from benzene–petroleum.

4-*Phenylindanone* (IV).—β-2-Diphenylylpropionic acid (2 g.) suspended in pure dry benzene (20 c.c.) was treated with phosphorus pentachloride (2 g.), shaken until solution of the acid was complete, and left at room temperature for one hour. The acid chloride, recovered after evaporation under reduced pressure, was dissolved in dry carbon disulphide (4 c.c.), powdered aluminium chloride (3 g.) was added, and the whole was left protected from moisture at 0° for 3 days. Dilute hydrochloric acid was added and after distillation in steam to remove the solvent the residual liquor was extracted with ether from which, when washed with dilute alkali, dried, and evaporated, a gum was recovered. The gum distilled at 130—135°/10 mm. (yield 75%) and crystallised in the receiver; recrystallisation from ethanol–water gave rectangular prisms of 4-*phenylindanone* (yield 45%), initially melting at 69°, but changing on storage to m. p. 86° (Found: C, 86·7; H, 5·6. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%), while the mother-liquor of the crystallisation was worked up as described below. 4-Phenylindanone formed a 2 : 4-*dinitrophenylhydrazone* (referred to as "A" below) as scarlet needles, m. p. 243—245° (decomp.), from acetic acid (Found: C, 65·1; H, 4·3. $C_{21}H_{16}O_4N_4$ requires C, 65·0; H, 4·1%), and a *semicarbazone* as colourless platelets, m. p. 225—229° (decomp.) from 2-ethoxyethanol (von Braun and Manz, *loc. cit.*, record m. p. 192°) (Found: C, 72·3; H, 5·6; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·9%).

Oxidation. A well-stirred emulsion of the indanone (IV) (0·2 g.) in a little dilute sodium hydroxide at 100° was treated portionwise with 6% aqueous potassium permanganate until the pink colour persisted. Excess of permanganate (2 c.c.) was now added and the whole was maintained at 100° for 1 hour. After acidification and treatment with sulphur dioxide the insoluble product was collected, washed with water, reprecipitated from alkali, and again collected. Sublimation at 120°/2 mm. furnished *3-phenylphthalic anhydride*, m. p. 145°, from benzene–petroleum (Found: C, 74·9; H, 3·5. $C_{14}H_8O_3$ requires C, 75·0; H, 3·6%), from which 3-phenylphthalic acid, m. p. 169—171°, was obtained on hydrolysis (Heilbron *et al.*, *J.*, 1938, 1386, give m. p. 181°). For identification, the latter was cyclised by warming for 10 minutes in concentrated sulphuric acid from which dilution with water yielded fluorenone-1-carboxylic acid, m. p. and mixed m. p. with an authentic specimen 190—191°, from ethanol–water.

*Detection of Dibenz*cyclo*heptadienone* (V).—The mother-liquor from the crystallisation of 4-phenylindanone gave a colourless gum on evaporation. (i) One portion of the gum (0·3 g.) in acetic acid (3 c.c.) was heated under reflux for 1 hour with a solution of sodium dichromate (1·3 g.) in acetic acid (3·5 c.c.). A chloroform extract of the diluted solution was washed with aqueous sodium hydroxide, dried, and concentrated. The gummy neutral residue gave crystals of phenanthraquinone, m. p. and mixed m. p. 204—205°, from chloroform (diazine, from *o*-phenylenediamine, m. p. and mixed m. p. 216—219°). The alkaline liquor gave, on acidification, diphenic acid, m. p. and mixed m. p. 216—219°. (ii) The residual gum (0·28 g.) was treated with 2 : 4-dinitrophenylhydrazine (0·3 g.) in ethanol–sulphuric acid and the well-washed precipitate was dissolved in the minimum quantity of hot acetic acid. On cooling, the aforementioned 2 : 4-dinitrophenylhydrazone "A", m. p. and mixed m. p. 243° (decomp.), crystallised, and the filtrate when kept overnight deposited a second dinitrophenylhydrazone, m. p. 230—233° (decomp.) depressed to 220—226° by admixture with "A". The residual mother-liquor was now concentrated to half its volume and was seeded with "A". After 2 hours the resulting deposit of slightly impure "A" was filtered off and the filtrate was then seeded with the second dinitrophenylhydrazone, of which a further crop accrued. The combined crops of the second material were crystallised from acetic acid, forming orange-red needles of m. p. 236—238° (decomp.) raised to 238—240° by admixture with the 2 : 4-dinitrophenylhydrazone of (V) (Cook, Dickson, and Loudon, *loc. cit.*) and depressed to 216—224° (decomp.) by admixture with "A".

Cyclisation of (III) *with Hydrogen Fluoride.*—The acid (III) (0·84 g.) was dissolved in hydrogen fluoride (*ca.* 10 c.c.) which was then allowed to evaporate in absence of moisture. The residue, after treatment with cold dilute sodium hydroxide, was recovered in ether and gave 4-phenylindanone (IV), m. p. and mixed m. p. 86—87°, from ethanol (yield 79%). The mother-liquor from the crystallisation gave, on concentration, a yellow gum which when oxidised (cf. above) with sodium dichromate in acetic acid afforded phenanthraquinone, m. p. and mixed m. p. 201—204°, after sublimation; diazine from *o*-phenylenediamine, m. p. and mixed m. p. 216—217°.

Cyclisation of β-(*5-Bromo-2* : *3* : *4* : *4′-tetramethoxy-6-diphenylyl*)*propionic Acid with Hydrogen Fluoride.*—The neutral solid (0·38 g.), obtained by treating (I) (1 g.) with hydrogen fluoride as above, was crystallised from petroleum (b. p. 40—60°) and gave, as first crop, warty nodules of the bromo-ketone (II) (0·014 g.), (micro-)m. p. and mixed m. p. 141·5°, which was debrominated to 5 : 6 : 7-trimethoxy-4-*p*-methoxyphenylindan-1-one (cf. Part VIII, *loc. cit.*), (micro-)m. p. and mixed m. p. 84—86°. This compound [oxime, (micro-)m. p. 216°] was also obtained as a second crop of needles from the petroleum mother-liquor of the bromo-ketone.

2 : 3 : 4-*Trimethoxydiphenyl-6-carboxylic Acid* (IX).—Methyl 3 : 4 : 5-trimethoxybenzoate (265 g.) and 1-phenyl-3 : 3-dimethyltriazen (53 g.) were slowly treated with acetic acid (70 c.c.) at 100° and the whole was heated at 100° for 16 hours. The resulting dark liquid, dissolved in chloroform, was thoroughly washed in turn with dilute hydrochloric acid, water, dilute sodium hydroxide, and again with water, and recovered. Unchanged ester was distilled off up to 185°/10 mm. and the residue was combined with similar residues obtained by renewed interaction of the recovered ester with fresh triazen. In all, 110 g. of the triazen were used in three runs and the crude trimethoxybenzoate finally recovered weighed 200 g. The combined higher-boiling residues on fractional distillation gave: (*a*) a small quantity of unchanged ester, b. p. 180—186°/10 mm.; (*b*) the main, partly solid fraction, b. p. 186—205°/10 mm.; (*c*) an oily fraction, b. p. 204—214°/10 mm. Fractions (*b*) and (*c*) when rubbed each with half its volume of methanol gave solids which were combined (24 g.) and crystallised from methanol (50 c.c.). The resulting crystalline mixture was swirled in the solvent, the lighter material (solid B) was collected by decantation, and the mother-liquor was used for renewed treatment of the heavier constituent. The latter, after further crystallisation from methanol, afforded *methyl* 2 : 3 : 4-*trimethoxydiphenyl-6-carboxylate* (15 g.), m. p. 71—72° (Found: C, 67·6; H, 5·7. $C_{17}H_{18}O_5$ requires C, 67·5; H, 5·95%), which was hydrolysed by 50% aqueous potassium hydroxide in methanol to the corresponding *acid* (IX), m. p. 196° from methanol (Found: C, 66·95; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%), and was regenerated from this acid by diazomethane in ether; m. p. and mixed m. p. 71—73°. The combined gums, recovered from the various methanol mother-liquors of the above separation, gave small additional quantities of the products after redistillation and re-treatment, while the final methanol mother-liquors on heating with aqueous alkali gave in addition to some non-saponifiable oil (discarded) a small quantity of the above acid, m. p. 191—193°.

Solid B (2·2 g.) was separated by crystallisation from methanol into a small, sparingly soluble fraction consisting of nacreous platelets, m. p. 210°, probably of *p*-terphenyl (Found: C, 93·6; H, 6·15. Calc. for $C_{18}H_{14}$: C, 93·9; H, 6·1%), and a relatively soluble fraction (1·5 g.) of m. p. 156° (Found: C, 70·6; H, 5·65. $C_{10}H_{16}O_4$ requires C, 70·6; H, 5·9%), which is probably *methyl* 2 : 6-*dimethoxydiphenyl-4-carboxylate* (cf. Part VIII, *loc. cit.*). The latter compound was hydrolysed by aqueous potassium hydroxide in methanol to the corresponding *acid*, m. p. 237° from methanol (Found: C, 69·8; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

2 : 3 : 4-*Trimethoxyfluorenone.*—The acid (IX) (0·3 g.) was dissolved and gently warmed (10 minutes) in thionyl chloride. The solvent was distilled off; the residual *ketone* formed long orange needles, m. p. 113°, from methanol (Found: C, 70·8; H, 5·2. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%). It yielded a 2 : 4-*dinitrophenylhydrazone* as fluffy red needles, m. p. 211°, from acetic acid (Found: C, 58·4; H, 3·8. $C_{22}H_{18}O_7N_4$ requires C, 58·7; H, 4·0%).

2 : 3 : 4-*Trimethoxydiphenyl*-6-*aldehyde* (XI).—2 : 3 : 4-*Trimethoxydiphenyl*-6-*carboxyhydrazide*, colourless needles of m. p. 156° from methanol (Found: C, 63·7; H, 5·9. $C_{16}H_{18}O_4N_2$ requires C, 63·8; H, 6·0%), was prepared by heating the methyl ester of (IX) (16·7 g.) and 90% hydrazine hydrate (31 c.c.) in methanol (60 c.c.) for 8 hours. Addition of benzenesulphonyl chloride (9·2 g.) to its solution in cold pyridine (14·1 g. in 84 c.c.), followed after 1 hour by pouring into iced hydrochloric acid, yielded the *benzenesulphonyl* derivative, m. p. 162—163° (from methanol) (Found: C, 59·4; H, 4·9. $C_{22}H_{22}O_6N_2S$ requires C, 59·7; H, 5·0%). A solution of the latter (18·5 g.) in ethylene glycol (150 c.c.) at 160° was treated with anhydrous sodium carbonate and, after 100 seconds, the reaction was quenched with boiling water. The required *aldehyde*, recovered from an alkali-washed ethereal extract, formed almost colourless plates, m. p. 92—93°, from methanol (Found: C, 70·6; H, 5·7. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

β-2 : 3 : 4-*Trimethoxy*-6-*diphenylylacrylic Acid* (XIII).—A solution of the above aldehyde (9·3 g.) and malonic acid (7·4 g.) in dry pyridine (20 c.c.) containing a few drops of piperidine was heated first at 100° (4 hours) and then under reflux (15 minutes). After cooling, pouring into iced hydrochloric acid, and extraction with ether, the required *acid* was recovered from aqueous alkali and formed small needles, m. p. 165°, from acetic acid–water (2 : 1) (Found: C, 68·7; H, 5·6. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%).

β-2 : 3 : 4-*Trimethoxy*-6-*diphenylylpropionic Acid* (XV).—This *acid* was prepared by hydrogenating a solution of (XIII) (9·6 g.) in acetic acid (330 c.c.) over palladium-black (0·6 g.). After filtration and recovery the acid formed colourless plates, m. p. 121—122°, from acetic acid–water (1 : 1) (Found: C, 68·7; H, 6·3. $C_{18}H_{20}O_5$ requires C, 68·7; H, 6·3%). Methylation with diazomethane in ether gave the *methyl* ester as cubes, m. p. 56°, from light petroleum (b. p. 40—60°) (Found: C, 69·3; H, 6·8. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7%).

5 : 6 : 7-*Trimethoxy*-4-*phenylindan*-1-*one*.—This *ketone* was obtained as neutral product in colourless needles of m. p. 74° from petroleum (b. p. 60—80°) (Found: C, 72·9; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%) when the acid (XV; 0·5 g.) was treated with hydrogen fluoride. It formed an *oxime*, m. p. 200°, from ethanol (Found: C, 68·9, H, 6·0. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%). Oxidation of the crude product gave no evidence of the formation of a coloured phenanthraquinone derivative.

β-(5-*Bromo*-2 : 3 : 4-*trimethoxy*-6-*diphenylyl*)*propionic Acid* (VII).—A solution of bromine (0·1 c.c.) in dry chloroform (2·5 c.c.) was added to a solution of (XV) (0·63 g.) in the same solvent (12·5 c.c.) and, after 3 hours at room temperature, the crude product was recovered from the (water-washed) solution. It was purified by conversion into the sparingly soluble sodium salt by concentrated aqueous sodium hydrogen carbonate. The *bromo-acid* was regenerated by dilute hydrochloric acid, forming colourless plates, m. p. 164—165°, from acetic acid–water (1 : 1) (Found: C, 54·7; H, 4·8. $C_{18}H_{19}O_5Br$ requires C, 54·7; H, 4·8%) and affording, with diazomethane in ether, the *methyl* ester, m. p. 95—96° (from methanol) (Found: C, 55·7; H, 5·0. $C_{19}H_{21}O_5Br$ requires C, 55·6; H, 5·1%).

Attempts to cyclise (VII).—(*a*) The neutral gum obtained from (VII) by treatment with hydrogen fluoride remained resinous after reaction with Girard's reagent-T and hydrolysis of the product. It afforded a bright red 2 : 4-dinitrophenylhydrazone, but was not converted into a solid by debromination with hydrogen in presence of palladised strontium carbonate. (*b*) The acid (0·7 g.) in dry benzene (10 c.c.) was shaken with phosphorus pentachloride (0·4 g.). Volatile materials were removed under reduced pressure and the residue was treated with carbon disulphide (3 c.c.) and aluminium chloride (0·6 g.). After 2 days at 0° dilute hydrochloric acid was added, the solvent was removed in steam, and the neutral product was recovered from chloroform as a gum. This did not yield a solid on debromination.

Neither of the (debrominated) gums showed any trace of a phenanthraquinone derivative when oxidised with sodium dichromate in acetic acid.

1-m-*Methoxyphenyl*-3 : 3-*dimethyltriazen*.—A diazo-solution from *m*-anisidine (100 g.), concentrated hydrochloric acid (290 c.c.), water (200 c.c.), and sodium nitrite (56 g.) was added with stirring to a mixture of 25% dimethylamine (280 g.) and 30% aqueous sodium carbonate (800 c.c.) kept at 0°; the mixture was then stirred for 30 minutes and the product was extracted in benzene and recovered from the dried extract. The *triazen* distilled as a yellow liquid (114 g.), b. p. 161°/15 mm. (Found: C, 60·4; H, 6·9. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·25%).

2 : 3 : 4 : 3′-*Tetramethoxydiphenyl*-6-*carboxylic Acid* (X).—Starting from methyl 3 : 4 : 5-trimethoxybenzoate (165 g.), the above triazen (32 g.), and acetic acid (43 c.c.) and using in all 125 g. of the triazen in 4 runs as described for (IX), there were obtained recovered initial ester (94 g.) and the following higher-boiling fractions: (*a*) a small fraction, b. p. 185—215°/8 mm.; (*b*) a main fraction, b. p. 203—220°/0·5 mm. On rubbing these combined fractions with half their volume of methanol there was obtained a product, regarded as *methyl* 2 : 6 : 3′-*trimethoxydiphenyl*-4-*carboxylate* (cf. Part VIII, *loc. cit.*), m. p. 154—156°, from acetic acid (yield, 2 g.) (Found: C, 67·5; H, 5·7. $C_{17}H_{18}O_5$ requires C, 67·5; H, 5·9%), which was hydrolysed by 50% potassium hydroxide in methanol to the corresponding *acid*, m. p. 215°, from acetic acid (Found: C, 65·9; H, 5·6. Found, after drying *in vacuo*/100° for 1 hour: C, 66·4; H, 5·2. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·5%), and was regenerated from this acid by diazomethane in ether. The methanol mother-liquor from the foregoing ester contained a second (oily) ester which was hydrolysed to 2 : 3 : 4 : 3′-*tetramethoxydiphenyl*-6-*carboxylic acid* (X), colourless prisms, m. p. 134—135° (19 g.), from methanol–water (1 : 1) (Found: C, 64·2; H, 5·8. $C_{17}H_{18}O_6$ requires C, 64·1; H, 5·8%).

2 : 3 : 4 : 6- *and* 2 : 3 : 4 : 8-*Tetramethoxyfluorenone*.—The residue obtained by heating (X) with thionyl chloride and distilling off excess of this reagent crystallised from methanol as a mixture of small lemon-coloured needles (A) and heavier, stout, golden needles (B). These were separated by swirling and decanting (A) with the mother-liquor. *Fluorenone*-A, m. p. 122° from methanol (Found: C, 68·1; H, 5·45. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%), afforded a 2 : 4-*dinitrophenylhydrazone* as fluffy red needles, m. p. 236° from acetic acid (Found: C, 57·6; H, 4·1. $C_{23}H_{20}O_8N_4$ requires C, 57·5; H, 4·2%). *Fluorenone*-B, m. p. 152—153° from methanol (Found: C, 68·2; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%), gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 137° depressed by admixture with the isomer (Found: C, 57·8; H, 3·7%).

2 : 3 : 4 : 3′-*Tetramethoxydiphenyl*-6-*aldehyde* (XII).—This *compound*, crystallising in colourless

plates, m. p. 60—61°, from methanol (Found : C, 67·4; H, 5·8. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%), and yielding a 2 : *4-dinitrophenylhydrazone*, m. p. 192° (Found : C, 57·4; H, 4·7. $C_{23}H_{22}O_8N_4$ requires C, 57·3; H, 4·6%), was prepared as described for (XI) *via* the *hydrazide*, m. p. 137—138° (Found : C, 61·6; H, 6·0. $C_{17}H_{20}O_5N_2$ requires C, 61·45; H, 6·0%), and *benzenesulphonhydrazide*, m. p. 182—183°, of the acid (X) (Found : C, 58·5; H, 5·0. $C_{23}H_{24}O_7N_2S$ requires C, 58·7; H, 5·1%). Under the conditions given, decomposition of the sulphonhydrazide was incomplete: the sulphonhydrazide was partly recovered from a chloroform extract of the reaction products by washing with 2N-sodium hydroxide, from which it was liberated by saturation with carbon dioxide and on renewed treatment yielded the aldehyde.

β-(2 : 3 : 4 : *3′-Tetramethoxy-*6*-diphenylyl)acrylic Acid* (XIV).—This *acid* which formed colourless needles, m. p. 150—151°, from acetic acid : water (1 : 1) (Found : C, 66·2; H, 5·8. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%), and the corresponding *propionic acid* (XVI), m. p. 90—91° (from dilute acetic acid) (Found : C. 65·7; H, 6·2. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%), were obtained by the methods described for analogous cases.

5 : 6 : 7-*Trimethoxy*-4-m-*methoxyphenylindan*-1-*one* was obtained as neutral product from the treatment of the acid (XVI) with hydrogen fluoride. It formed thick colourless plates, m. p. 141—142°, from methanol (Found : C, 69·25; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). An oxidation test on the cyclised material gave no evidence of formation of a phenanthraquinone derivative.

β-(*5-Bromo-2* : 3 : 4 : *3′-tetramethoxy-6-diphenylyl)propionic Acid* (VIII).—The *bromo-acid,* m. p. 163—164° (from acetic acid) (Found : C, 53·8; H, 4·8. $C_{19}H_{21}O_6Br$ requires C, 53·65; H, 5·0%), was prepared from (XVI) as described for the compound (VII).

5 : 6 : 7-*Trimethoxy-4-(?-bromo-*m*-methoxyphenyl)indan*-1-*one.*—Colourless plates, m. p. 115—116° (from methanol) (Found : C, 56·1; H, 4·7. $C_{19}H_{19}O_5Br$ requires C, 56·0; H, 4·7%), of this *ketone* were obtained as neutral product by treating (VIII) with hydrogen fluoride. The gum, recovered from the methanol mother-liquor, did not afford evidence of formation of a phenanthraquinone derivative when oxidised with sodium dichromate in acetic acid.

Debromination. The above bromo-indanone (0·04 g.) in methanol (20 c.c.) was shaken (1 hour) with 2% palladised strontium carbonate in an atmosphere of hydrogen. Concentration of the filtered solution yielded 5 : 6 : 7-trimethoxy-4-*m*-methoxyphenylindan-1-one, m. p. and mixed m. p. 139—141°.

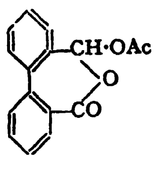
2 : *5-Dimethoxydiphenyl-2′-carboxylic Acid* (XVII).—Glacial acetic acid (60 c.c.) was slowly added to a melt of quinol dimethyl ether (160 g.) and 1-(*o*-carbomethoxyphenyl)-3 : 3-dimethyltriazen (50 g.; cf. Elks and Hey, *J.*, 1943, 443) at 100° and the mixture was maintained at this temperature for 18 hours. The resulting dark liquid was dissolved in chloroform and, after being washed in turn with dilute hydrochloric acid, water, dilute sodium hydroxide and again with water, the solution was dried and concentrated. Distillation of the residue gave the following fractions : (i) quinol dimethyl ether (140 g.), b. p. 110—112°/10 mm.; (ii) a pale yellow oil (3 g.), b. p. 127—132°/10 mm.; (iii) a yellow oil (7 g.), b. p. 196—204°/10 mm., which when rubbed with methanol gave *methyl* 2 : *5-dimethoxydiphenyl-2′-carboxylate*, m. p. 65° from methanol (Found : C, 70·6; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%); (iv) a viscous brownish gum, b. p. 205—215°/10 mm. with much decomposition, yielding a small quantity of unidentified needles, m. p. 291—293°, when rubbed with methanol; (v) a non-volatile residue which was dissolved in chloroform, washed with dilute hydrochloric acid and, combined with the residues from subsequent runs, concentrated, and redistilled, thereby slightly adding to fraction (iv). Fraction (ii), combined with the methanol mother-liquors from fractions (iii) and (iv), gave on hydrolysis (1 hour) with aqueous methanolic potassium hydroxide the *acid* (XVII), m. p. 155° (from methanol), which was also obtained by hydrolysing the pure methyl ester (Found : C, 69·9; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

2-*Hydroxy-5-methoxydiphenyl-2′-carboxylic Acid Lactone* (XVIII).—The preceding acid (0·5 g.) in benzene (5 c.c.) and thionyl chloride (1·2 c.c.) was kept for 12 hours at room temperature. After removal of solvent under reduced pressure (temp. *ca.* 25°), the lactone was obtained as colourless crystals, m. p. 119—120°, from benzene (Found : C, 73·7; H, 4·4; OMe, 13·4. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·4; OMe, 13·7%). It did not give a coloration to aqueous ferric chloride, was insoluble in cold alkali, but dissolved on heating and was regenerated on acidification.

Monobenzenesulphonhydrazide of Diphenic Acid.—(*a*) A suspension of the monohydrazide of diphenic acid (1·3 g.; m. p. with gas evolution 185° : cf. Labriola, *Chem. Zentr.*, 1938, II, 1770) in cold pyridine (4 c.c.) was treated with benzenesulphonyl chloride (0·9 g.) which was washed in with the aid of a further 2 c.c. of pyridine. After 12 hours at room temperature the yellow solution was added to dilute sulphuric acid, yielding the required *product*, m. p. 220° from ethanol–water (Found : C, 60·3; H, 4·1; N, 7·3. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·0; N, 7·1%). With acetic anhydride and a trace of sulphuric acid or with acetic anhydride in pyridine it reacted to form an *anhydro-acetyl* derivative, m. p. 216° from acetic acid, which was insoluble in alkali (Found : C, 63·3; H, 3·9; N, 6·5. $C_{22}H_{16}O_5N_2S$ requires C, 62·9; H, 3·8; N, 6·7%).

(*b*) Diphenic anhydride (6·6 g.) was added slowly with cooling to a solution of benzenesulphonhydrazide (5·1 g.) in pyridine (30 c.c.). After 12 hours the solid obtained on pouring into dilute hydrochloric acid yielded the above compound, m. p. and mixed m. p. 220°, from ethanol–water, as main product, while a second product—probably the isomeric *aa-diacylhydrazide* [$C_{12}H_8(CO_2H){\cdot}CO{\cdot}N(NH_2)SO_2Ph$]—m. p. 220° depressed to *ca.* 215° by admixture with the above compound, was obtained in small amount from the mother-liquor (Found : C, 60·8; H, 4·0; N, 6·9. $C_{20}H_{16}O_5N_2S$ requires C, 60·6; H, 4·0; N, 7·1%).

2′-Formyldiphenyl-2-carboxylic Acid (XIX).—To a solution of the above benzenesulphonhydrazide (2 g.; main fraction) in ethylene glycol (20 c.c.) at 165° anhydrous sodium carbonate (25 g.) was added during 30 seconds and after a further 240 seconds the reaction was terminated by cautious addition of boiling water (100 c.c.). After cooling and filtering, unreacted hydrazide was precipitated by a stream of sulphur dioxide, and the resulting mother-liquor, on acidification with dilute sulphuric acid, gave the *acid* (XIX) in 40% yield, m. p. 132° from methanol–water (Found : C, 74·5; H, 4·4. $C_{14}H_{10}O_3$ requires C, 74·4; H, 4·4%).



ω-Acetoxydiphenide (as annexed) was obtained when a solution of (XIX) in acetic anhydride containing a few drops of concentrated sulphuric acid was kept for 12 hours and then poured into water. After recovery from an alkali-washed ethereal extract, the neutral product had m. p. 125° from methanol (Found: C, 71·6; H, 4·3. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). It was reconverted into (XIX) by warming (90 minutes) in dilute sulphuric–acetic acid.

β-(2′-Carboxy-2-diphenylyl)acrylic Acid (XX).—A solution of the aldehydo-acid (XIX) (1·2 g.) and malonic acid (0·55 g.) in pyridine (6 c.c.), containing a few drops of piperidine, was heated first at 100° (1 hour) and then under reflux (15 minutes) before being cooled and poured into dilute hydrochloric acid. The oily product soldified and had m. p. 228° [Rapoport and Williams, *loc. cit.*, record m. p. 230—231° (corr.)], from dilute acetic acid (Found: C, 72·1; H, 4·5. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%). Its titre, determined in methanol solution, showed the compound to be dibasic (Found: equiv., 130. Calc.: equiv., 134).

β-(2′-Carboxy-2-diphenylyl)propionic Acid (XXI).—The above acid, dissolved in acetic acid, was hydrogenated in presence of palladium-black at ordinary temperature and pressure. Hydrogenation was complete in 1½ hours and the product, recovered from the filtered solution, had m. p. 185° from aqueous acetic acid (Found: C, 71·1; H, 4·8. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%). Rapoport and Williams (*loc. cit.*) give m. p. 171—173° (corr.) (prepared by three distinct methods).

Cyclisation of (XXI).—(*a*) The dry barium salt, heated in a sublimation apparatus at 360°/1 mm., yielded an oily sublimate which could not be induced to crystallise but afforded a 2 : 4-dinitrophenylhydrazone, (micro-)m. p. 220° from acetic acid, unchanged by further crystallisation or by admixture with the 2 : 4-dinitrophenylhydrazone of (V), (micro-)m. p. 237°. (*b*) The dry sodium salt (0·11 g.) was heated under reflux with acetic anhydride (2 c.c.) for 1 hour. The solvent was removed under reduced pressure and the residue was treated with dilute alkali and extracted with ether. The oil recovered from the ether yielded a crystalline 2 : 4-dinitrophenylhydrazone, (micro-)m. p. 234° and mixed m. p. 235° with the 2 : 4-dinitrophenylhydrazone of (V).

p-*Tolyl* 2-o-*carboxyphenylthiolbenzoate* was prepared by heating (90 minutes) a solution of diphenic anhydride (0·5 g.) and thio-*p*-cresol (0·34 g.) in pyridine at 70°. It solidified when the cooled solution was poured into dilute hydrochloric acid and had m. p. 147° (from methanol–water) (Found: C, 72·8; H, 4·6. $C_{21}H_{16}O_3S$ requires C, 72·4; H, 4·6%). On cooling a solution of the compound in warm dilute sodium hydroxide there was deposited a crystalline product of m. p. 88°, from which the thiol-ester was regenerated by dilute acid and which appeared to be a hydrated *sodium* salt (Found: C, 51·6; H, 5·5. $C_{21}H_{15}O_3SNa,7H_2O$ requires C, 51·6; H, 5·8%).

When treated as in the following case with Raney nickel the half thiol-ester yielded 2′-hydroxymethyldiphenyl-2-carboxylic acid, m. p. 145—146° [from ether–light petroleum (b. p. 40—60°)], which was converted by heating at 110° for 1 hour into diphenide, m. p. and mixed m. p. 132° (Kenner and Turner, *J.*, 1911, **99**, 2101, give m. p.s 146° and 132°, respectively).

p-*Tolyl* o-*Carbomethoxythiolbenzoate*.—A solutión of equivalent amounts of *o*-carbomethoxybenzoyl chloride and thio-*p*-cresol in cold pyridine was poured, after 12 hours, into iced dilute hydrochloric acid. The product, washed with alkali, dried, recovered in ether, and crystallised from methanol, had m. p. 58—59° (Found: C, 67·3; H, 4·9. $C_{16}H_{14}O_3S$ requires C, 67·1; H, 4·9%). A solution of this compound (1·5 g.) in 70% ethanol (30 c.c.) was heated under reflux with suspended Raney nickel (7·5 g.) for 90 minutes. After filtration, concentration, and an ineffective attempt to separate aldehydic material by means of sodium hydrogen sulphite solution, the resulting oil slowly solidified, giving crystals of m. p. and mixed m. p. with phthalide 71—72°.

p-Tolyl thiolbenzoate (2 g.) in 70% ethanol (40 c.c.) with Raney nickel (10 g.) in suspension was heated under reflux for 6 hours. On distillation from a water-bath the ethanol entrained some benzaldehyde, isolated as 2 : 4-dinitrophenylhydrazone (0·25 g.), m. p. and mixed m. p. 235°, whilst the residue afforded benzyl alcohol (0·25 g.), b. p. 178°/24 mm., characterised as the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 110—112°.

Ethyl thiolbenzoate (9·5 g.) in 70% ethanol (180 c.c.) was heated under reflux with Raney nickel (54 g.) for 2 hours. The filtrate from the nickel was diluted with water and extracted with ether. The ether was removed through an efficient reflux column and the residue was cautiously treated with an excess of concentrated nitric acid, nitration being completed by heating under reflux for 1 hour. Nitrobenzene was isolated by distillation, b. p. 208—210°, and was identified by conversion (Raney nickel and hydrogen) into aniline, b. p. 180—182°, and thence into acetanilide and tribromoaniline. The yield of benzene, based on the aniline found, was 60%.

p-*Tolyl* 3 : 4 : 5-*Trimethoxythiolbenzoate*.—Thio-*p*-cresol (2·6 g.) in dry pyridine (14 c.c.) was treated with finely powdered 3 : 4 : 5-trimethoxybenzoyl chloride and the whole was heated at 80° for 1 hour. The cooled mixture was poured into iced hydrochloric acid and, after recovery in benzene, the *thiol*-ester formed colourless plates, m. p. 102° (Found: C, 64·2; H, 5·4. $C_{17}H_{14}O_4S$ requires C, 64·35; H, 5·4%).

Reaction with Raney Nickel.—(i) The thiol-ester (2·25 g.) in 70% ethanol (50 c.c.) containing Raney nickel (12 g.) in suspension was heated under reflux for 6 hours. After recovery and distillation there were obtained: (i) 1 : 2 : 3-trimethoxybenzene (0·24 g.), b. p. 80°/0·5 mm., m. p. 42—43° from petroleum (b. p. 40—60°), forming a *picrate*, golden needles of m. p. and mixed m. p. 79—80° (Found: C, 45·8; H, 3·8; N, 10·4. $C_{15}H_{15}O_{10}N_3$ requires C, 45·4; H, 3·8; N, 10·6%), and further characterised by oxidation with dilute nitric acid to 2 : 6-dimethoxybenzoquinone, m. p. 246—248°; (ii) 3 : 4 : 5-trimethoxybenzyl alcohol (0·62 g.), b. p. 152—154°/0·5 mm., identified as the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 147—148° (Cook, Graham, and Cohen, *J.*, 1944, 323) (Found: C, 52·3; H, 4·15. Calc. for $C_{17}H_{16}O_9N_2$: C, 52·1; H, 4·1%).

(ii) The thiol-ester (4 g.) in dioxan (40 c.c.) was treated with a suspension of Raney nickel (32 g.) in dioxan (40 c.c.). Heat was evolved and the reaction was completed by shaking for 1 hour at room temperature. 1 : 2 : 3-Trimethoxybenzene (0·705 g.) and 3 : 4 : 5-trimethoxybenzyl alcohol (1·05 g.) were again isolated as under (*a*).

Ethyl 3 : 4 : 5-*trimethoxythiolbenzoate* (7 g.), b. p. 185°/0·3 mm., m. p. 35—36° from light petroleum

(b. p. 40—60°) (Found : C, 56·3 ; H, 6·3. $C_{12}H_{16}O_4S$ requires C, 56·3 ; H, 6·25%), treated as in experiment (i), gave 1 : 2 : 3-trimethoxybenzene (1·1 g.) and 3 : 4 : 5-trimethoxybenzyl alcohol (2·1 g.).

We thank the Carnegie Trust for the Universities of Scotland for a scholarship (to G. T. D.) and the Department of Scientific and Industrial Research for Maintenance Allowances (to J. J., J. MacM., and W. F. W.). Microanalyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, September 22nd*, 1949.]

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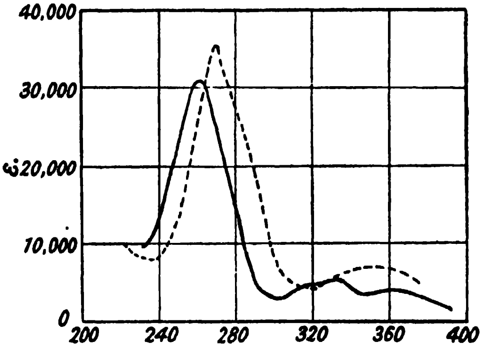
31. *The Structure of Stipitatic Acid.*

By R. E. CORBETT, A. W. JOHNSON, and A. R. TODD.

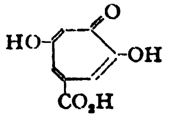
Oxidation of stipitatic acid with alkaline hydrogen peroxide gives a mixture of aconitic and malonic acid, indicating that stipitatic acid is 6(4)-hydroxytropolone-4(6)-carboxylic acid (I or II).

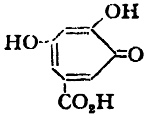
STIPITATIC ACID, $C_8H_6O_5$, was isolated from the culture media of *Penicillium stipitatum* Thom by Birkinshaw, Chambers, and Raistrick (*Biochem. J.*, 1942, **36**, 242), who carried out a number of degradative experiments but were unable to advance a satisfactory structural formula. The compound was optically inactive, contained no *C*-methyl groups but had three active hydrogen atoms, and it titrated as a dibasic acid. On acetylation, two isomeric diacetyl derivatives were obtained, both soluble in sodium carbonate solution, and on methylation two isomeric trimethyl derivatives were formed, both neutral and insoluble in cold dilute aqueous sodium hydroxide. Other derivatives of stipitatic acid which were described included a dimethyl compound, soluble in dilute sodium hydroxide but insoluble in sodium hydrogen carbonate, formed from it by the action of hot methanolic hydrogen chloride or from disodium stipitatate by methyl iodide; a dibasic monomethyl derivative obtained by treatment of the acid with methyl sulphate in the presence of methanolic potassium hydroxide; and finally a monobromo-substitution product prepared by bromination in aqueous acetic acid. This bromo-derivative titrated as a dibasic acid and gave a neutral compound, "bromotrimethylstipitatic acid," on methylation with diazomethane. These facts indicated the presence of two enolic (or phenolic) groupings of varying acid strengths and one carboxyl group, whose presence was confirmed by decarboxylation of stipitatic acid to give a compound, $C_7H_6O_3$, which was monobasic and gave a blood-red precipitate with ferric chloride. Although no evidence was obtained for the presence of a free carbonyl group, hydrogenation in the presence of platinum, or reduction with zinc and acetic acid, gave products which gave positive carbonyl reactions, and this suggested the presence of a masked carbonyl group in stipitatic acid. The five oxygen atoms were thus accounted for in two enolic hydroxyl groups, one carboxyl and one masked carbonyl group. The titratable acidity of reduced stipitatic acid was one-half that of the original acid, presumably owing to the reduction of the acidic enolic group. A most important observation was made on fusing stipitatic acid or its monomethyl derivative with potassium hydroxide at 300°, when 5-hydroxy*iso*phthalic acid was obtained in good yield. No satisfactory structure was advanced to explain all of these findings and, in particular, a dihydroxyformylbenzoic acid structure was shown to be untenable. The similarity in the general behaviour of stipitatic acid and puberulic acid, noted by Raistrick and his colleagues, is further emphasised by the similarity of their ultra-violet absorption spectra (see figure).



Ultra-violet absorption spectra of puberulic (-----) *and stipitatic acid* (——) *in aqueous solutions.*

In 1945, Dewar (*Nature*, **155**, 50) re-examined the above evidence and suggested that stipitatic acid was probably the hydroxytropolonecarboxylic acid (I), or the tautomeric form (II), although no further experimental evidence was provided. Nevertheless, Dewar showed that such a structure would offer a satisfactory explanation of the various reactions described by Birkinshaw, Chambers, and Raistrick (*loc. cit.*). Thus the isomeric trimethyl compounds are derived from (I) and (II) and the dimethyl derivative is probably methylated on the carboxyl and ketol groups, the acidity being due to the remaining enolic grouping. The formation of 5-hydroxy*iso*phthalic acid was ascribed to a benzilic acid type of rearrangement


(I.)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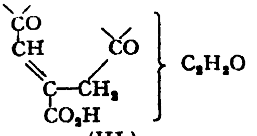
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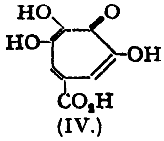
(IV.)

of the tropolone ring and this view is supported by more recent work on tropolone derivatives (*e.g.*, Barltrop and Nicholson, *J.*, 1948, 116; Erdtman and Gripenberg, *Acta Chem. Scand.*, 1948, **2**, 625; Cook and Somerville, *Nature*, 1949, **163**, 410).

We have now obtained degradative proof that structure (I) correctly represents stipitatic acid, for oxidation with alkaline hydrogen peroxide at room temperature gives a mixture of aconitic and malonic acid. The isolation of aconitic acid indicates that stipitatic acid can be represented by (III), and as a benzenoid structure has been shown to be untenable, the only feasible structure for the molecule is (I) or the tautomer (II). Since it has been shown (Corbett, Johnson, and Todd, *J.*, 1950, 6) that puberulic acid is represented by (IV) or one of its tautomeric forms, this acid can be regarded as a hydroxy-stipitatic acid; that this might prove to be the case was originally suggested by Dewar (*Nature*, 1945, **155**, 479).

Further evidence in favour of structure (I) is obtained by the periodate oxidation of hydrogenated stipitatic acid, 0·85 mole of reagent being consumed, indicating the presence of a 1 : 2-diol structure; in the course of this experiment we confirmed that the titratable acidity of stipitatic acid is halved after reduction.

EXPERIMENTAL.

Stipitatic acid was prepared from cultures of *P. stipitatum* Thom as described by Birkinshaw, Chambers, and Raistrick (*loc. cit.*).

Oxidation of Stipitatic Acid with Hydrogen Peroxide.—Stipitatic acid (1·5 g.) was dissolved in aqueous sodium hydroxide (30 c.c. of N.), hydrogen peroxide (14 c.c. of 31%) added, and the mixture left for 72 hours at room temperature, the solution changing from orange-red to pale golden-yellow. This solution was acidified with hydrochloric acid (32 c.c. of N.) (evolution of carbon dioxide), and the mixture evaporated at 50°/13 mm. and dried *in vacuo* over phosphoric oxide. The colourless, rather gummy residue was continuously extracted with dry ether for 9 hours, and the extract was then evaporated giving a white solid contaminated with some colourless resin (100 mg.). The white solid was dissolved in dry ether (5 c.c.), and light petroleum (b. p. 40—60°) was added at the b. p. until a faint cloudiness was produced. The solution, set aside at 0° for 24 hours, deposited small colourless prisms (30 mg.), m. p. 186—187°. The m. p. was not raised by recrystallisation from ether–light petroleum and was unchanged on admixture with authentic aconitic acid (m. p. 186—187°) (Found : C, 41·5; H, 3·5. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·5%).

Under the conditions of the fluorescein reaction, the oxidation product gave, with resorcinol–sulphuric acid, a red solution with a pale greenish-yellow fluorescence in daylight, and a beautiful sky-blue fluorescence in ultra-violet light, identical with that observed using authentic aconitic acid. With pyridine and acetic anhydride it showed the same series of colour changes as authentic aconitic acid.

The mother-liquors, after removal of the aconitic acid, were again brought to the b. p. and a further quantity of light petroleum added to induce further crystallisation. The solution was set aside at 0° for 24 hours, and a further crop of somewhat less pure aconitic acid (20 mg.), m. p. 160—165°, collected. The mother-liquors were evaporated to dryness, and the white residue (50 mg.) sublimed at 80—85°/10^{-5} mm. giving a colourless micro-crystalline sublimate (21 mg.), m. p. 120—125°, and leaving behind a residue of slightly impure aconitic acid, m. p. 178—179°. The sublimate was purified by resublimation at 80°/10^{-4} mm. and formed small colourless prisms, m. p. 131—133°, which had m. p. 134—135° when mixed with malonic acid (m. p. 135—136°) (Found : C, 34·7; H, 4·4. Calc. for $C_3H_4O_4$: C, 34·6; H, 3·8%). The identity of this product with malonic acid was confirmed by the identity of their colour changes with acetic anhydride and by treatment with resorcinol–sulphuric acid under the conditions of the fluorescein reaction, both giving orange-red solutions with a yellow fluorescence in daylight and a pale greenish-blue fluorescence in ultra-violet light.

Periodate Oxidation of Reduced Stipitatic Acid.—Stipitatic acid (616 mg.) was dissolved in dry methanol (75 c.c.) and hydrogenated at atmospheric pressure using Adams's platinum catalyst, 4·6 moles of hydrogen being absorbed. Aliquots of the methanolic solution, titrated before and after reduction, required 13·3 c.c. and 6·37 c.c. of N/100-alkali, respectively. Removal of the methanol under reduced pressure left a colourless gum, which was exactly neutralised with N-sodium hydroxide and extracted continuously with ether for 9 hours. Evaporation of the ethereal extract yielded only a trace of a neutral gum which gave no reaction with Brady's reagent. Reduced stipitatic acid was regenerated from its sodium salt by passage through a pre-treated resin column and, after removal of the water by evaporation under reduced pressure, was obtained as a colourless gum (376 mg.). A solution of this reduced stipitatic acid in water was oxidised with sodium periodate; it consumed 0·85 mole of oxidising agent.

Light Absorption.—An aqueous solution of puberulic acid showed maxima at 2700 and 3500 A.; $\varepsilon_{max.}$ 35,200 and 7160. An aqueous solution of stipitatic acid showed maxima at 2620, 3320, and 3600 A.; $\varepsilon_{max.}$ 30,800, 5150, and 4050 respectively.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October* 10*th*, 1949.]

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32. *The Deamination of Amino-acids by Nitrous Acid with Particular Reference to Glycine. The Chemistry underlying the Van Slyke Determination of α-Amino-acids.*

By A. T. AUSTIN.

The deamination of α-amino-acids by nitrous acid, which is the basis of the Van Slyke gasometric method for the determination of amino-acids, is not, as is generally considered, accurately described (for the example of glycine) by the equation :

$$H_3N^+{\cdot}CH_2{\cdot}CO_2^- + HNO_2 \longrightarrow HO{\cdot}CH_2{\cdot}CO_2H + N_2 + H_2O$$

In the case of glycine the gas evolved is a mixture of nitrogen, carbon dioxide, and nitrous oxide, and increases in volume with increasing nitrite-ion concentration. There is a corresponding decrease in the amount of glycollic acid in the reaction residue, and from this residue nitromethane and methyl nitrolic acid have been isolated. These facts are explained by the assumption that in the deamination process an intermediate is formed which can interact with negative ions, such as chloride or nitrite ions (giving α-substituted acids), or with water molecules (giving α-hydroxy-acids). By nitrite-ion interaction it appears that α-nitroacetic acid is formed in the above reaction, and it has been shown that this acid may either decompose to nitromethane and carbon dioxide or react with nitrous acid to give methylnitrolic acid and carbon dioxide. At pH 4—5 methylnitrolic acid is converted into a polymer of fulminic acid with much frothing. This polymer breaks down to formohydroxamic acid, and it is shown that, under the above experimental conditions, 10% of this decomposes to cyanic acid and 90% to formic acid and hydroxylamine. The latter with nitrous acid gives nitrous oxide. An explanation is thus obtained for the anomalous gas volumes and troublesome frothing encountered in the Van Slyke nitrous acid determination of glycine.

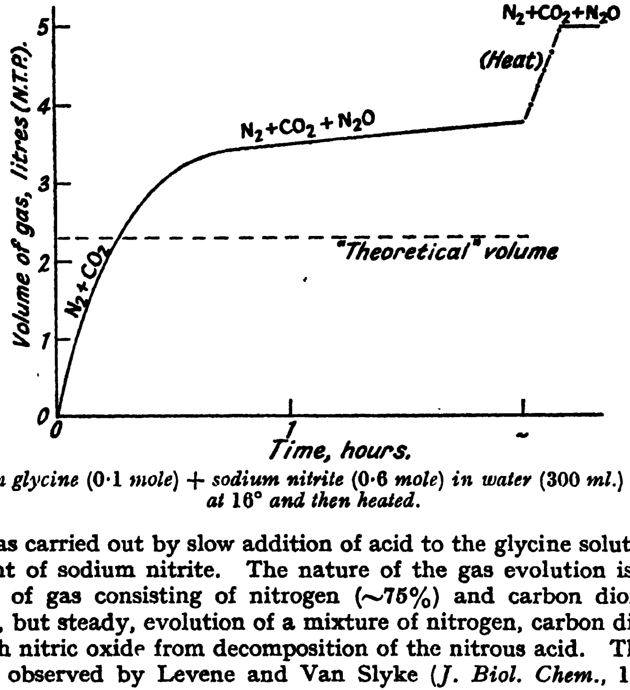
THE analytical determination of aliphatic amino-groups by the reaction with nitrous acid and measurement of the volume of nitrogen liberated presents an anomaly with α-amino-acids: this is that the volume of gas obtained is greater, in varying degree, than is indicated by the equation :

$$H_3N^+{\cdot}CHR{\cdot}CO_2^- + HNO_2 \longrightarrow HO{\cdot}CHR{\cdot}CO_2H + N_2 + H_2O \quad . \quad . \quad . \quad . \quad (1)$$

It was in connexion with α-amino-acids that the special advantages of the procedure developed by Van Slyke (*J. Biol. Chem.*, 1911, **9**, 185; 1912, **12**, 275; 1929, **83**, 425) were most useful; but the uncertainty arising from the fact that "too much" nitrogen was evolved, together with a considerable amount of carbon dioxide, and that extensive frothing often occurred, made it apparent that the reaction was not adequately described by equation (1). Several of the amino-acids that gave anomalous gas volumes contained other NH_2-groups (amido) or peptide linkages (that could react after splitting); and, in the absence of analytical determination of the products, it was impossible to say that the excess of gas did not arise from this source. However, this uncertainty does not exist with glycine (and other monoamino-acids all the nitrogen in which is evolved), so that the excess of gas must have its origin connected in some way with the nitrite ion or nitrous acid. Van Slyke was of the opinion that the diazo-intermediate postulated could decompose in two ways, to give either the hydroxy-compound or, by total disruption of the molecule, carbon dioxide and "some other gas." Later investigators (Schmidt, *J. Biol. Chem.*, 1929, **82**, 587; Lough and Lewis, *ibid.*, 1934, **104**, 601; Kendrick and Hanke, *ibid.*, 1937, **117**, 161; 1940, **132**, 739; Viscontini, *Helv. Chim. Acta*, 1946, **29**, 1491) considered that oxidation by the nitrous acid was the source of the carbon dioxide, the nitrous acid being reduced to nitrogen. It has been suggested by others that nitrous acid de-amination may be a more complex reaction than is indicated by equation (1), and Treves and Salomone (*Biochem. Z.*, 1908, **7**, 11) and Dunn and Lewis (*J. Biol. Chem.*, 1921, **49**, 327) observed the red colour of the alkaline solution after the deaminising of certain proteins. In the absence of further data they were unable to suggest the nature of these secondary reactions. The present paper is confined to the general chemistry of the reaction of nitrous acid with glycine, and forms part of an investigation dealing with the mechanism and products of nitrous acid–amine reactions.

A clue to the more detailed behaviour of the nitrous acid reaction with α-amino-acids was obtained during a study of the reaction of methylamine with nitrous acid (to be published later). It was found that an appreciable amount of nitromethane could be isolated. It was postulated, by analogy, that under similar conditions the corresponding α-nitro-carboxylic acid may be formed in reaction (1); and it is well known that such compounds are readily decarboxylated to yield nitroparaffins. Moreover, such α-nitro-acids would be expected to be very reactive to nitrous acid, and it seemed plausible that this was the cause underlying the anomalous behaviour of the α-amino-acids and, in particular, the source of the carbon dioxide. Although the present investigation has been confined to the first member of the series, glycine, considerable support was given to the above postulate when it was found that the greater the nitrite-ion concentration in the reacting solution the greater was the excess of evolved gas over the amount predicted by equation (1). Furthermore, the reaction residue became red when made alkaline; this colour could be discharged on acidification, and ether-extraction from the acid solution yielded pale yellow needles of methyl nitrolic acid.

FIG. 1.



Evolution of gas from glycine (0·1 *mole*) + *sodium nitrite* (0·6 *mole*) *in water* (300 *ml.*) *when slowly acidified at* 16° *and then heated.*

The reaction was carried out by slow addition of acid to the glycine solution containing the appropriate amount of sodium nitrite. The nature of the gas evolution is shown in Fig. 1. A rapid evolution of gas consisting of nitrogen (~75%) and carbon dioxide (~25%) was followed by a slow, but steady, evolution of a mixture of nitrogen, carbon dioxide, and *nitrous oxide*, together with nitric oxide from decomposition of the nitrous acid. This slow secondary gas evolution was observed by Levene and Van Slyke (*J. Biol. Chem.*, 1912, **12**, 285) and Schmidt (*loc. cit.*), although its nature was not investigated. Initially the reaction solution is almost colourless, but, on the addition of acid, it quickly develops a reddish-brown colour, which soon becomes green. In order to accelerate the slow gas evolution the reaction products were heated after 2—3 hours. When heated, the solution became very dark green, and much gas was evolved. The solution then suddently became paler—to a reddish-orange, and finally to a very pale yellow—and the gas evolution ceased. The final volume of gas obtained is shown by the broken line in Fig. 1. A pronounced odour of hydrogen cyanide was always observed after this final heating.

With greater concentrations of sodium nitrite the phenomena were essentially the same, but the volume of gas obtained was considerably increased, particularly that of carbon dioxide. These results are shown in Table I.

Considerable frothing occurred during reaction at the two higher nitrite concentrations and it was with some difficulty that this was controlled at the highest concentration. This moderately stable froth, which tends to cause the reaction contents to pass over into the gas-collecting apparatus, is discussed below.

TABLE I.

Gas evolution (N.T.P.) *when* 80 *ml. of hydrochloric acid* (2·0N.) *are slowly added to glycine* (0·1 *mole*) *and sodium nitrite* (*x mole*) *in* 300 *ml. of water. Theoretical volume according to equation* (1), 2·24 *l.*

Amount of glycine, mole.	Initial amount of NaNO$_2$ = *x*, mole.	N$_2$, l.	CO$_2$, l.	N$_2$O, l.	$\frac{\text{N}_2\text{ (expt.)}}{\text{N}_2\text{ (theor.)}}$	$\frac{[\text{Nitrite}]}{[\text{Glycine}]}$
0·100	0·300	2·45	0·69	0·32	1·09	3
0·100	0·600	2·68	0·97	0·37	1·19	6
0·100	1·200	2·72	1·13	0·45	1·23	12

The amount of glycollic acid in the residues showed a progressive decrease, corresponding to the anomalous results described above; these results are contained in Table V.

When the reaction between glycine and nitrous acid was carried out in the cold with very slow generation of nitrous acid it was possible to isolate nitromethane by distillation and fractionation of the residue. If, however, the acid was added at all rapidly, nitromethane could not be isolated and ether-extraction of an unheated portion of the solution yielded pale yellow crystals of methylnitrolic acid (together with a yellow oil—see below). This behaviour was consistent with that of nitroacetic acid, as was directly shown by experiment. The successful isolation of the products of the self-decomposition of nitroacetic acid on the one hand, and also of the products of its reaction with nitrous acid on the other, confirms beyond reasonable doubt its formation in the above reaction. It has not, however, been possible to isolate nitroacetic acid from the reaction mixture, for the above reasons, and in order to check the hypothesis further and at the same time obtain an estimate of the amount of nitro-acid formed, the empirical method was adopted of running a solution of synthetically prepared nitroacetic acid into a solution of sodium nitrite which was being slowly acidified. In this way one would be imitating the abnormality postulated in the glycine reaction, and one would look for all the abnormal behaviour observed in this reaction, *viz.*, (1) excessive yield of nitrogen, (2) the formation of carbon dioxide and nitrous oxide, (3) the striking colour changes: colourless ⟶ reddish-brown ⟶ dark green, and, on heating, very dark green ⟶ reddish-orange ⟶ pale yellow, (4) the extensive frothing, (5) the strong odour of hydrocyanic acid on distillation and fraction of the residues. The duplication of behaviour was exact. Table II shows the quantities of gas evolved when potassium nitroacetate reacts with nitrous acid and the resultant solution is heated.

TABLE II.

Potassium nitroacetate, g.	N$_2$, l.	CO$_2$, l.	N$_2$O, l.
4·00	0·22	0·58	0·26
6·00	0·26	0·80	0·30
Cf. the result of the reaction of glycine (0·1 mole) and sodium nitrite (0·3 mole):	0·21 *	0·69	0·32

* Excess of nitrogen, unaccounted for on basis of equation (1).

This reaction of the nitroacetate ion with nitrous acid may be formulated as follows:

$$\mathrm{O_2N{\cdot}CH_2{\cdot}CO_2H + HNO_2 \longrightarrow [O_2N{\cdot}C({:}N{\cdot}OH){\cdot}CO_2H] \longrightarrow O_2N{\cdot}CH{:}N{\cdot}OH + CO_2} \quad . \quad (2)$$

The intermediate oximino-compound is immediately decarboxylated to give methylnitrolic acid, which then gives rise to nitrogen, carbon dioxide, and nitrous oxide, as shown below. The initial reaction in equation (2) probably involves the *aci*-form of the nitroacetate ion, as appears to be the case with other similar nitrosations, *e.g.*, the reaction of nitromethane with nitrous acid. When the reaction with nitroacetic acid was carried out at 0°, carbon dioxide was quantitatively evolved in accordance with equation (2), and ether-extraction of the solution yielded crystals of methylnitrolic acid together with the yellow oil—again in agreement with the behaviour with glycine. This oil is being further investigated; but it is thought to be dinitromethane, obtained from the oxidation of the methylnitrolic acid.

A reaction similar to that represented by equation (2) was observed by Ponzio (*Gazzetta*, 1903, **33**, I, 510). The action of dinitrogen tetroxide dissolved in ether on oximinoacetic acid caused decarboxylation, to give methylnitrolic acid. It would seem that the unstable intermediate postulated above is formed in this reaction too:

$$\mathrm{HO{\cdot}N{:}CH{\cdot}CO_2H \xrightarrow{N_2O_4} [HO{\cdot}N{:}C(NO_2){\cdot}CO_2H] \longrightarrow HO{\cdot}N{:}CH{\cdot}NO_2 + CO_2}$$

Jovitschitsch (*Ber.*, 1895, **28**, 1213) isolated the ester of this unstable intermediate by the action of nitric acid (*d* 1·2) on ethyl oximinoacetoacetate.

Attention was next directed to the reactions of methylnitrolic acid, in order to determine the contributions of this substance to the reactions. In alkaline solution it has a red colour, which is destroyed on acidification. Wieland (*Ber.*, 1907, **40**, 418) has shown that this acid decomposes into fulminic acid and nitrous acid, and suggested the intermediate formation of the unstable isomeric nitrile oxide, $H-C\equiv N\rightarrow O$. By slow addition of alkali to an ice-cold solution of methylnitrolic acid he obtained a white precipitate which he formulated as a cyclic polymer of this isomer of fulminic acid and called trifulmin (*ibid.*, 1909, **42**, 808). If, however, the alkali is added to the solution at room temperature (20—25°) very extensive frothing occurs, and this has been shown to take place at pH 4—5. The above solutions of glycine and sodium nitrite, and of potassium nitroacetate and sodium nitrite are buffered approximately to this pH, and it is thus easy to understand the frothing. Wieland showed that in acid solution trifulmin was converted into formic acid and hydroxylamine hydrochloride, and, in alkaline solution, into cyanic acid; and he postulated the intermediate formation of formohydroxamic acid, $HO{\cdot}CH{:}N{\cdot}OH$, which he detected by colour tests with ferric ions (cherry-red) and cupric ions (green). Table III shows the quantities of gas evolved when a solution of synthetically prepared methylnitrolic acid was run into a solution of sodium nitrite that was being slowly acidified. The froth formed was vigorously stirred into solution. The striking colour changes noted above were again observed, and also the odour of hydrocyanic acid after the heating of the solution.

TABLE III.

Methylnitrolic acid, g.	N_2, l.	CO_2, l.	N_2O, l.
1·40	0·17	0·20	0·17
3·38	0·40	0·39	0·44

The dual mode of decomposition of formohydroxamic acid led to similar experiments being carried out on synthetically prepared acid, in order to determine the relative proportions of the two modes under the experimental conditions used, and also to ascertain the fate of the decomposition products in the nitrous acid solution. This decomposition of formohydroxamic acid may be represented:

$$NH_3 + CO_2 \longleftarrow HNCO \longleftarrow HO{\cdot}CH{:}N{\cdot}OH \longrightarrow H{\cdot}CO_2H + NH_2{\cdot}OH$$

The data in Table IV show the quantities of gas obtained when a solution of formohydroxamic acid is heated with an acid sodium nitrite solution (as in the experiments with glycine, with potassium nitroacetate, and with methylnitrolic acid).

TABLE IV.

Formhydroxamic acid, g.	N_2, l.	CO_2, l.	N_2O, l.
1·53	0·26	0·04	0·34

As expected, the cyanic acid formed in the reaction immediately decomposes to carbon dioxide and ammonia, the latter with nitrous acid then giving nitrogen. By a similar reaction part of the hydroxylamine gives nitrous oxide, and part decomposes to nitrogen and ammonia (which with nitrous acid gives nitrogen). The formic acid remains unchanged and may be detected by its reducing properties.

Most of the carbon dioxide obtained in the glycine reactions comes, therefore, from the decarboxylation of the nitrosated nitroacetic acid, and estimates were made on this basis, with the help of the data of Table II, of the amounts of nitro-acid formed in the different glycine–sodium nitrite solutions. These amounts are shown in Table V (col. 3), and compared with the analytical determinations of glycollic acid in the residues (col. 4).

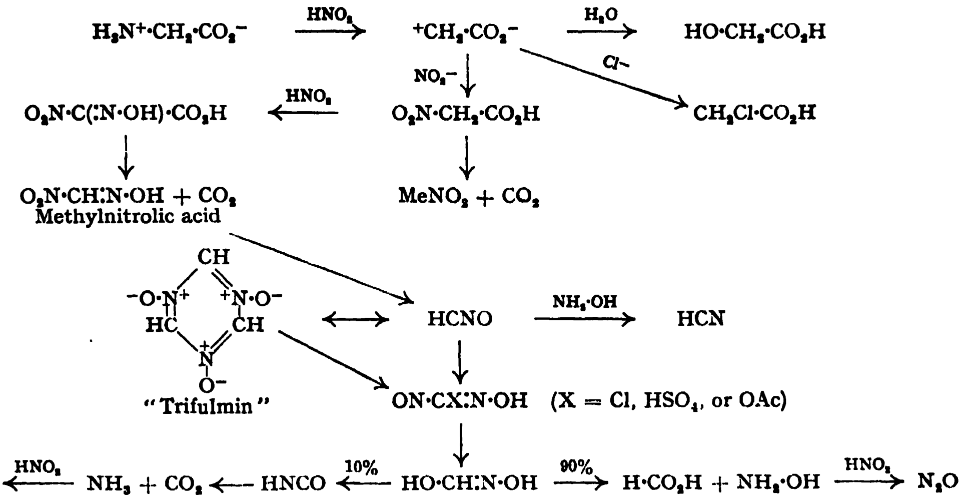
TABLE V.

Glycine, mole.	Initial, $NaNO_2$, mole.	Nitroacetic acid, mole.	Glycollic acid, mole.
0·100	0·300	0·03	0·055
0·100	0·600	0·04	0·039
0·100	1·200	0·05	0·032

The accumulated evidence now permits co-ordination of the behaviour observed when glycine reacts with nitrous acid in the presence of nitrite ion. The sequence of reactions may be formulated as shown in the reaction chart.

The detailed mechanism of the process involved in the removal of the NH_3-group has yet to be confirmed, but steps leading to a carbonium ion are postulated, and glycollic acid would be formed by interaction of this ion with water molecules. The carbonium ion may also react with negative ions in solution to give nitroacetic acid (which then undergoes the series of changes represented) or chloroacetic acid (which has been isolated), by interaction with nitrite and chloride ions, respectively. It would be expected that the greater the ionic concentration the greater would be the amount of substituted acid formed and, as shown in Table I, this has been found in the case of solutions containing varying amounts of nitrite ion.

In the reaction scheme the nitroacetic acid is represented as reacting with nitrous acid with *subsequent* decarboxylation, and not as undergoing preliminary decarboxylation followed by reaction of the nitromethane with the nitrous acid to give methylnitrolic acid. The reason



$H_3N^+{\cdot}CH_2{\cdot}CO_2^-$
HNO_2
$^+CH_2{\cdot}CO_2^-$
H_2O
$HO{\cdot}CH_2{\cdot}CO_2H$
NO_2^-
Cl^-
$O_2N{\cdot}C(:N{\cdot}OH){\cdot}CO_2H$
HNO_2
$O_2N{\cdot}CH_2{\cdot}CO_2H$
$CH_2Cl{\cdot}CO_2H$
$O_2N{\cdot}CH:N{\cdot}OH + CO_2$
Methylnitrolic acid
$MeNO_2 + CO_2$
"Trifulmin"
HCNO
$NH_2{\cdot}OH$
HCN
$ON{\cdot}CX:N{\cdot}OH$ ($X = Cl, HSO_4$, or OAc)
N_2
HNO_2
$NH_3 + CO_2$
HNCO
10%
$HO{\cdot}CH:N{\cdot}OH$
90%
$H{\cdot}CO_2H + NH_2{\cdot}OH$
HNO_2
N_2O

is that decarboxylation of nitroacetic acid is comparatively slow at 0° (and even at 20°), whereas in the presence of nitrous acid the carbon dioxide is liberated immediately. The nature of this reaction, which is used as a test for nitroacetic acid, does not appear to have been previously considered in detail.

The reaction solutions always developed a green colour, which was more intense the lower the temperature and the higher the nitrite-ion concentration. It was at first thought that methylnitrosolic acid ($ON{\cdot}CH:NOH$, from HONC and HNO_2) was the cause of the colour. This acid is known to be green and to decompose to formohydroxamic acid (Wieland and Hess, *Ber.*, 1909, **42**, 4175). However, methylnitrosolic acid is easily extracted by ether (to give a green extract), whereas the green colour in the glycine, nitroacetic acid, and methylnitrolic acid reaction solutions could not be removed in this way. Therefore, it appeared that the colour might be that of the anion of a more acidic nitroso-compound. The moderately stable green colour was obtained irrespective of the acid used (hydrochloric, sulphuric, acetic). When, however, hydrochloric acid was added in excess of that required for reaction the green colour became deep blue. This colour could easily be extracted by ether. On drying of the ethereal extract the colour changed to emerald-green. Evaporation of the ether under reduced pressure yielded a green oil, which was explosive at room temperature, and from its reactions was considered to be a chloronitroso-compound. Its constitution has yet to be confirmed. The green oil becomes blue when added to water, and, on addition of alkali, olive-green. These colour changes are reversible. This suggested that the green colour of the reaction solution might be caused by the ion of the chloronitroso-compound, $ON{\cdot}CCl:NO^-$ (which would be stabilised by resonance). With sulphuric and with acetic acid the anions formed would be $ON{\cdot}C(HSO_4):NO^-$ and $ON{\cdot}C(OAc):NO^-$, respectively. It is assumed that in these cases the free (un-ionised) acids are too unstable to exist in visible concentration. [Nef found that $CHCl:N{\cdot}OH$ is much more stable than $CH(HSO_4):N{\cdot}OH$; *Annalen*, 1894, **280**, 316.] The blue colour of the aqueous reaction solutions and the behaviour of the green oil were observed whenever hydrochloric acid was used in the treatment of glycine, nitroacetic acid, or methylnitrolic acid with nitrous acid. The gas evolutions were, however, independent of the acid employed.

The white solid obtained by Wieland (*loc. cit.*) on addition of alkali to methylnitrolic acid is very explosive when dry, and is insoluble in all ordinary solvents. Wieland considered it to be a trimer of an isomer of fulminic acid, and assigned to it a cyclic structure by analogy with the structures accepted at that time for cyanuric acid and cyamelide. In the light of present knowledge it seems that the properties of this substance would be more consistent with a straight-chain indefinite polymer $[\cdot CH{:}N^{+}(\cdot O^{-})\cdot]_n$. The froth obtained in the experiments with glycine (cf. p. 150) appeared to be gas, from decomposition of part of the solid, enclosed in liquid films stabilised by the unchanged dispersed solid. As such it was difficult to suck dry on the filter funnel but, when dry, it had the same explosive properties as the more easily filtered substance obtained at 0° from methylnitrolic acid. One of the difficulties encountered in the Van Slyke determination of amino-acids by nitrous acid is the extensive frothing that often occurs, which tends to carry the reactants into the gas-measuring compartments. The cause of this was previously unknown, and octan-2-ol is added in these determinations in an attempt to diminish this trouble (Peters and Van Slyke, "Quantitative Clinical Methods," Vol. II, p. 385, Williams and Williams, Baltimore, Md., 1932). As shown above, the pH at which methylnitrolic acid changes to this polymer is about 4—5. The pH in a Van Slyke determination is in this range, and it is thus easy to see that any methylnitrolic acid formed during a glycine determination will lead to frothing.

The formation of hydrogen cyanide in all cases, starting from glycine, nitroacetic acid, or methylnitrolic acid, undoubtedly owes its origin to the oxidising properties of the unstable isomer of fulminic acid, and is correlated with the observation of Wieland (*loc. cit.*) that trifulmin and hydroxylamine gave hydrogen cyanide. Nef (*Annalen*, 1894, **280**, 330) and Schischkoff (*Annalen*, 1861, Suppl. Vol. **1**, 108) have also observed the formation of hydrogen cyanide from fulminic acid in reducing media.

It is clear that ion interaction is the determining factor causing the deviations from equation (1); and, in the usual procedure the anion involved is the nitrite ion. The subsequent changes that the nitroacetic acid thus formed may undergo allow an essentially complete explanation to be drawn up for the manifold series of changes observed in the glycine–nitrous acid reaction. The reaction is more disturbed by interaction with nitrite ion than by that with chloride ion; for the latter, forming chloroacetic acid, may eventually yield the expected hydroxy-compound, whereas the nitroacetic acid, being so reactive to nitrous acid, results in extensive changes. Although it has generally been asserted that oxidation was the source of the carbon dioxide, it now appears safe to dismiss oxidation as the disturbing factor, for oxidation of amino-groups is not easy in acid solution and, moreover, the carbon dioxide is evolved from the commencement of the reaction. Also, very little nitric oxide ($<1\%$) is in the first part of the evolved gas. This gas contains some 25% of carbon dioxide and, if oxidation were the cause of this, much more nitric oxide would be expected. It was also shown by experiment that a large excess of nitrous acid was without effect on the amount of carbon dioxide, and that the deviation of behaviour from equation (1) depended on the nitrite ion and not on the nitrous acid.

In order to minimise this nitrite ion effect (and at the same time check again the above postulates) the procedure was adopted of running the nitrite solution slowly into an acid-glycine solution. The results obtained are summarised in Table VI. When the solution was acidified with hydrochloric acid the carbon dioxide was evolved in about 10% of its former quantity; but when acetic acid was employed, whilst less carbon dioxide was evolved, the quantity was considerably more than when hydrochloric acid was used. This was as expected; for the equilibrium

TABLE VI.

Sodium nitrite solution slowly added to glycine (0·1 *mole*) *and* 0·12M-*acid in water* (300 *ml.*).

Acid.	N_2, l.	CO_2, l.
HCl	1·75	0·065
HCl	1·91	0·056
HOAc	2·24	0·234

$$HOAc + NO_2^- \rightleftharpoons HNO_2 + OAc^-$$

lies very much to the left, and therefore much free nitrite ion is present in such a system.

The Van Slyke determination is carried out by mixing three solutions: saturated aqueous sodium nitrite, acetic acid, and the solution containing the amine. Acetic acid is used for two reasons. First, it causes less decomposition of nitrous acid—for the above-mentioned reason that very little free nitrous acid exists in these solutions. Nitrite ion is thus in excess, and so it causes the anomalous behaviour described. Secondly, amides, urea, etc., which are usually present in biological extracts, evolve nitrogen much less readily in the absence of mineral acid. Therefore attempts to minimise the disturbances caused by nitrite ion intervention by adding the nitrite solution to the amino-acid solution acidified with mineral acid (Table VI) would be unsatisfactory.

It was also noted that very little nitrous oxide was evolved when a glycine–sodium nitrite solution was rapidly acidified. This was due to the removal of nitrous acid from the solution (free nitrous acid rapidly decomposes). The hydroxylamine was shown to be held in solution as the hydrochloride.

From the foregoing, it is clear where the discrepancy lies in the Van Slyke determination of glycine. Although only one amino-acid has been studied here, it seems probable that the above series of reactions will apply in principle to a α-amino-acids generally, although the influence of adjacent groups in the higher members has yet to be ascertained. This influence may manifest itself with the higher amino-acids, such as alanine, etc., mainly by virtue of the reduction in the number of α-hydrogen atoms. The changes subsequent to the formation of nitro-compound may be impeded and nitrosation, which is so important in the rapid decarboxylation of glycine (p. 153), may not be possible. The amount of gas evolved with alanine, etc., is very close to that predicted by equation (1) and so permits the use of the Van Slyke determination, but it is almost certain that corresponding nitro-compounds are formed to a large extent and so the chemistry of the change is not represented by this equation. Glycine has always been recognised as one of the amino-acids least suitably determined by this method, and many attempts have been made to remove the anomaly of "too much" nitrogen. Kendrick and Hanke (*J. Biol. Chem.*, 1937, **117**, 161) claimed that the addition of potassium iodide or iodine eliminated the excess of nitrogen. This was disputed by Dunn and Porush (*ibid.*, 1939, **127**, 261) but reiterated by Kendrick and Hanke (*ibid.*, 1940, **132**, 739). They considered that the effect was caused by preferential oxidation by the iodine (with the result that nitrous acid was not reduced to nitrogen); but in view of the established nature of the glycine reaction it would be better to defer an explanation of the iodine effect until the reaction of iodine with the now known intermediates has been established.

The present investigation gives an explanation of the abnormal kinetic results of Abel, Schmid, and Sidon (*Z. Elektrochem.*, 1933, **39**, 863) in their investigation of glycine; it was found that as the nitrite-ion concentration was increased the velocity coefficient of the reaction increased several-fold. This was attributed to specific electrolyte effect on the amphoteric glycine (carbon dioxide was not tested for in the evolved gas, all of which was assumed to be nitrogen).

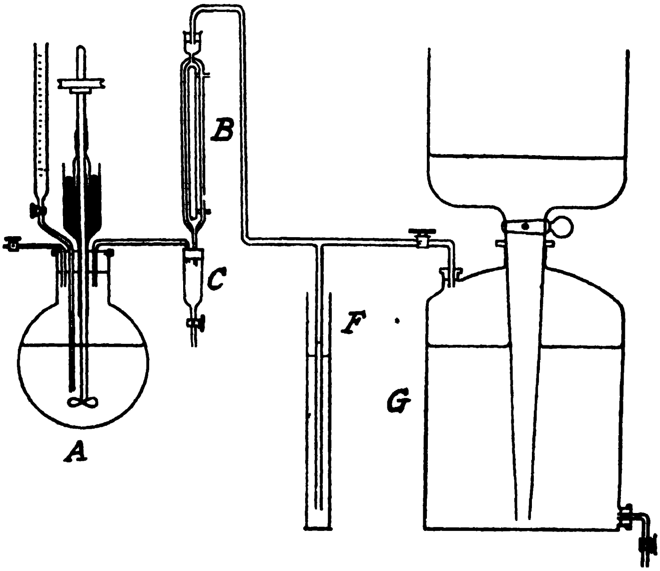
Viscontini (*Helv. Chim. Acta*, 1946, **29**, 1491) found that reaction of nitrous acid with polyglycines, such as glycylglycine, yielded very little of the expected hydroxy-compound, $HO{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$, but a large amount of oxalylglycine, $HO_2C{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$. The evolved gas contained very little carbon dioxide, but the nitrogen was 160% of that expected from the usual equation. These facts may now be interpreted on the assumption that the corresponding nitro-compound is formed, followed by nitrosation, giving $O_2N{\cdot}C({:}N{\cdot}OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$ which decomposes to oxalylglycine. It seems probable that nitrous oxide formed part of the gas evolved, but this was not tested.

It may be asked: "Where does the sequence of reactions stop under the conditions of the Van Slyke determination of glycine?" No proper answer can be given, but the considerable frothing that occurs indicates that part, at least, of the nitrolic acid has reached and passed the trifulmin stage. Concerning the gas evolution it may be said that there is a very rapid primary evolution of nitrogen (nitrous acid elimination of the amino-group of the amino-acid) accompanied by a fast evolution of carbon dioxide (from decarboxylation of the nitrosated nitro-acid). The secondary nitrogen and carbon dioxide, as well as the nitrous oxide, are formed at the end of the series of reactions (p. 153) and, at ordinary temperatures, this gas evolution is comparatively slow. The specified time in a Van Slyke determination is about 4 minutes (according to the temperature), and it can only be said that the stage reached in the gas evolution will at this time be somewhere just after the steep part of the curve in Fig. 1.

EXPERIMENTAL.

The apparatus used for measuring the gas evolution is shown in Fig. 2. Glycine (0·1 mole) and the appropriate amount of sodium nitrite were dissolved in water (300 ml.) in the flask *A* immersed in the thermostat. The whole apparatus was filled with nitrogen from a cylinder, and then standard acid (2N.) was slowly added from the burette (time of addition approx. 40 minutes). The evolved gas was collected in *G* over saturated aqueous sodium chloride, which was also saturated with the relevant gases. After a fixed interval of time (2—3 hours in different experiments) the thermostat was removed and the contents of flask *A* were heated to boiling. The ice-coldwater-condenser *B* retained steam, and this condensate was collected in the container *C*. Hydrochloric, sulphuric, and acetic acid were used and no difference was observed (other than the blue colour when hydrochloric acid was used). The preliminary reaction (*i.e.*, before the heating) was carried out at 0°, 16°, or 25°, again with no significant difference (although the green colour that developed was more intense the lower the temperature) and 16° was chosen for convenience in the final investigation.

FIG. 2.



The gas analyses were carried out on samples (35—45 ml.) taken from the gas collectors and brought into contact successively with small volumes of concentrated absorbents in gas-burettes. Acid ferrous sulphate was used to remove nitric oxide, potassium hydroxide for carbon dioxide, and ethyl alcohol for nitrous oxide. The residual gas was assumed to be nitrogen. Tests for carbon monoxide were negative. Because of its solubility in most reagents the presence of nitrous oxide makes the analyses somewhat uncertain, but by the use of small volumes of concentrated reagents the error due to this was kept low. That the gas removed by the ethyl alcohol was nitrous oxide was proved by passing the original gas (after removal of nitric oxide and carbon dioxide) through a trap immersed in liquid air. A white solid was retained. On removal of the trap from the liquid air this white solid melted to a colourless liquid which boiled at a very low temperature, and the evolved gas remained colourless in the presence of oxygen. Samples were evaporated into a eudiometer, mixed with hydrogen (1·8—2·5 volumes), and exploded according to the method of Menzel and Kretzschmar (*Z. angew. Chem.*, 1929, **42**, 148). The contractions observed were exactly equal to the original volume of gas sample: $N_2O + H_2 \longrightarrow H_2O + N_2$.

Materials.—Glycine used in the above experiments was recrystallised from aqueous alcohol and contained no detectable impurities. Analysis by the Sörensen formaldehyde method gave results identical with 3 other samples of AnalaR glycine.

Potassium nitroacetate was prepared from nitromethane (Steinkopf and Kirchhoff, *Ber.*, 1909, **42**, 3925) and, when recrystallised several times (50% aqueous potassium hydroxide) and washed with ethyl alcohol, was pale yellow. It was quite stable when kept *in vacuo*. It proved more convenient to use the potassium salt rather than the free acid, the preparation of which required the extra steps given by Pedersen (*Trans. Faraday Soc.*, 1927, **23**, 316). The acid, after recrystallisation from chloroform, melted at 93—93·5° (lit., 87—89°).

Methylnitrolic acid was prepared from nitromethane by the method of Wieland (*loc. cit.*). It is an unstable compound, m. p. 64—66° (decomp.), and could not be kept for more than a few hours. The aqueous solution soon decomposed and the gas measurements obtained with this (Table III) are not as decisive as those obtained using potassium nitroacetate.

Formohydroxamic acid, prepared from ethyl formate and hydroxylamine (Jones, *Amer. Chem. J.*, 1898, **20**, 28), formed white glistening plates, m. p. 80°.

Isolation of Nitromethane from the Glycine–Nitrous Acid Reaction.—The success of this experiment depends on the very slow addition of acid to the glycine–sodium nitrite solution in order to avoid a local excess of nitrous acid and so to enable the nitroacetic acid to decompose to nitromethane. Glycine (0·5 mole) and sodium nitrite (4 mole) in water (500 ml.) were slowly acidified (150 ml. of 2N-sulphuric acid) during 3 hours. An hour after completion of the acidification the solution was distilled. Oily droplets were visible in the early portions of the distillate, and distillation was continued until 150 ml. were collected. The distillate was neutralised and then fractionated using an ordinary disc-column. Between 75° and 95° a colourless 2-phase liquid was collected (total volume, 10 ml.). The lower phase ($\sim$2·5 ml.) was separated. With nitrous acid it gave the nitrolic acid test for nitromethane and, after being dried ($MgSO_4$), had b. p. 100—102° (micro-method) (nitromethane has b. p. 101°) (Found: C, 20·1; H, 5·5; N, 22·4. Calc. for CH_3O_2N: C, 19·7; H, 4·9; N, 22·9%). The refractive index was identical with that of a carefully purified specimen of nitromethane.

Isolation of Methylnitrolic Acid from the Glycine–Nitrous Acid Reaction.—The reaction was carried out at 0° with moderately quick addition of acid, taking precautions to keep the temperature low. The solution was extracted twice with ether, the extract dried ($CaCl_2$), and the solvent removed under reduced pressure. Pale yellow needles ($\sim$2 g.), m. p. 64—66°, were obtained from a solution of glycine (0·4 mole) and sodium nitrite (1·2 moles) in 300 ml. of water when acidified by 300 ml. of 2N-sulphuric acid; the m. p. and reactions were identical with those of synthetically prepared methylnitrolic acid. About 5—10 ml. of a yellow oil were also obtained in the extraction (cf. p. 151). On increase of the concentration of sodium nitrite in the above experiment, there was a marked increase in the amounts of yellow solid and oil, but these experiments at higher nitrite concentrations were difficult to control because of the extensive frothing.

Identical behaviour was observed when potassium nitroacetate was used in place of glycine. Pale yellow needles, m. p. 64—66° (decomp.), and a yellow oil were obtained on ether-extraction of the reaction residue.

Formation of Trifulmin.—The white froth that formed at ordinary temperatures in both the glycine and the potassium nitroacetate experiments could be filtered off; it had the same explosive character as the substance prepared from methylnitrolic acid (Wieland, *loc. cit.*). With methylnitrolic acid the frothing was shown to commence at pH 4—5.

Isolation of Chloroacetic Acid from the Glycine–Nitrous Acid Reaction when Chloride Ions were present.—Glycine (0·3 mole), sodium nitrite (0·32 mole) and potassium chloride (2·0 moles) were dissolved in water (500 ml.), and 150 ml. of acid (2N.) were slowly added during 2 hours. The temperature was kept at 5°. The blue colour of the final solution was readily removed with ether, and the colourless solution was then extracted with several further lots of ether. These extracts were dried ($CaCl_2$). Evaporation of the ether yielded 11·9 g. of white crystalline material. This had an odour similar to that of acetic acid, contained "bound" chlorine, and, after recrystallisation from chloroform, had m. p. 63°, undepressed on admixture with chloroacetic acid. The material boiled without decomposition at 187—189°/765 mm. (Found: C, 25·6; H, 3·3; Cl, 37·4. Calc. for CH_3O_2Cl: C, 25·4; H, 3·2; Cl, 37·6%). The amount of recovered chloroacetic acid represents a 40% conversion of the original glycine.

Analytical Determination of Glycollic Acid in the Glycine–Nitrous Acid Residues.—The acid–alkaline permanganate method suggested by Wieland and Franke (*Annalen*, 1927, **457**, 13) with the recommendations of Bottger and Oesper ("Newer Methods of Volumetric Chemical Analysis," Van Nostrand, N.Y., 1938) was found satisfactory. It was shown, using potassium nitroacetate, that most of the products other than glycollic acid could be removed by treatment with excess of nitrous acid followed by boiling (to remove formic acid). It was shown, using glycollic acid (Kahlbaum), that the above treatment resulted in the decomposition of approx. 10% of the glycollic acid, but it was considered that the method was sufficiently accurate for the present purpose.

Other Identifications.—Hydrocyanic acid was detected in the distillates by the characteristic odour, and the white precipitate obtained with silver nitrate (soluble in ammonia, insoluble in nitric acid) darkened on addition of mercurous nitrate (dissolving in excess). Prussian blue was obtained by heating with ferrous sulphate in alkaline solution. The pungent odour obtained on continued distillation (and fractionation) was established as due to formic acid by the solubility of the silver salt of the latter, and its reduction of ammoniacal silver nitrate. Hydroxylamine was detected in the residues by its reducing properties (mercuric chloride), and the formation of ammonia on heating of the alkaline solution.

The author is much indebted to Professor C. K. Ingold, F.R.S., and Professor E. D. Hughes, F.R.S., for their constant help and advice; and he records his gratitude to the University of Melbourne for the award of a Travelling Scholarship and to the Trustees of the Ramsay Memorial Fellowship Trust for a Fellowship which enabled an investigation, of which this work forms part, to be continued.

SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.
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33. *A Kinetic Study of Organic Inhibitors of the Reaction between Magnesium and Acids.*

By R. Hurst and M. A. Jermyn.

This paper extends to the system magnesium–acid, previous observations by other authors of the inhibition of metal–acid reactions by organic substances and presents simplified methods for studying the kinetics of such inhibitions.

The dissolution of magnesium by acids has been found to be inhibited by organic amines. The dissolution reaction is of zero order in the presence of excess of acid, with an energy of activation of about 4000 cals./g.-mol. which is not greatly altered by the presence of inhibitor. Various reaction-rate constants have been determined. The relation between inhibitor concentration and degree of inhibition is found to be that expected for an adsorption process. The effectiveness of the inhibitor depends on steric factors—the shape and size of its molecule regarded as adsorbed on the metal surface at an active point.

It has long been known that certain organic compounds can inhibit the attack on metallic surfaces by acids and other corroding agents. Investigations have been made into the inhibiting properties of a variety of substances, ranging from simple aliphatic amines to large colloidal molecules, chiefly with a view to practical application. From this body of data the following widely-accepted generalisations have been drawn. First, organic inhibitors act only in so far as they are adsorbed on the metal surface, since it is found that the activity of the inhibitor in depressing the reaction rate when expressed as a function of its concentration is a typical adsorption isotherm (Mann, Lauer, and Hultin, *Ind. Eng. Chem.*, 1936, **28**, 159, 1046). The presence of an adsorbed film of organic base has actually been demonstrated in one case (Rhodes and Kuhn, *ibid.*, 1929, **21**, 1066). Further, compounds having inhibitor properties are either colloidal electrolytes or molecules which form co-ordination complexes (*e.g.*, amines, ethers, thio-compounds, unsaturated hydrocarbons). Secondly, closely related compounds, though held to the metallic surface by the same active group, have widely different inhibiting powers. These differences may be explained by steric factors—an inhibitor molecule blankets an area of the metallic surface dependent on its shape and size.

Very little work has been done to elucidate the exact mechanism of these inhibitions; indeed, there is still no general agreement on the mechanism of the primary reaction between metals and acids which, like many heterogeneous reactions, has complicated kinetics unless simplifying conditions are chosen. It is only under similar simplified conditions that we can hope to obtain an insight into the mechanism of the inhibited reaction. A simple molecule as the inhibitor and a highly electropositive metal dissolving in a dilute strong acid provide the simplest conditions possible and help the theoretical analysis of the problem even though efficient "inhibition" in the practical sense is not achieved.

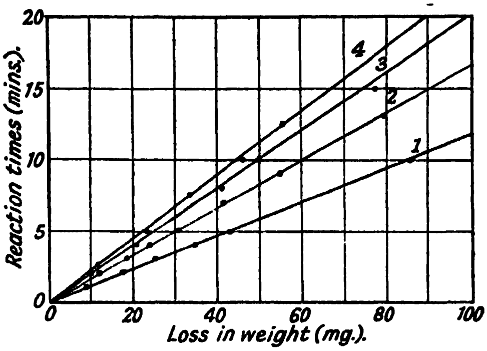
EXPERIMENTAL.

Hollow cylinders of magnesium, 2·0 cm. long and 0·9 cm. in diameter, were turned from rods of the pure metal. The preparation of the surface was found to be the most important single factor affecting reproducibility of the rate constants. Chemically etched surfaces gave erratic results and only mechanically polished surfaces were satisfactory. The cylinder was cleaned from oxide and grease and then polished with superfine emery paper. Particles of abrasive and metal were swabbed off with cotton-wool moistened with alcohol. Re-preparation of the surface was necessary after each run, especially when strongly inhibiting solutions were used. Reproducibility of ±2% was obtained with the same cylinder when prepared in this way. After being weighed, a prepared cylinder was secured to an ebonite rod passing through it by ebonite nuts and rubber washers at each end, and the whole was screwed together tightly so that only the external cylindrical surface was exposed. The rod was held vertically in a chuck which could be rotated at high speed through gearing from a constant-speed motor and which could be raised and lowered while rotating. The corrosive solution (500 c.c.) was placed in a bolt-head flask immersed in a thermostat kept at the desired temperature to within ±0·05°, and allowed to come to bath temperature. The motor was then started, and after reaching constant speed the rod and cylinder were lowered into the solution. At the end of the reaction period the rod was raised and a stream of water played on the cylinder as it slowed down. The detached cylinder was then washed thoroughly with distilled water, dried in a stream of warm air, and weighed. The raising and lowering of the cylinder occupied less than a second each in the usual total time of four minutes.

According to various workers (King and Cathcart, *J. Amer. Chem. Soc.*, 1937, **59**, 63; King and Schack, *ibid.*, 1935, **57**, 1212; Durdin and Markovitch, *J. Gen. Chem. Russia*, 1936, **6**, 236; Kilpatrick and Rushton, *J. Physical Chem.*, 1930, **34**, 2180), the reaction in the presence of a large excess of acid is of zero order. To check this under our conditions the same cylinder, freshly prepared each time, was rotated for various periods in an acid solution. Results obtained in a sodium acetate–hydrochloric acid mixture (pH = 1·09; see Walpole, *Biochem. J.*, 1914, **8**, 637) in 0·1N-acetic acid and in 0·1N-sulphuric acid are shown graphically in Fig. 1. In each case the loss in weight is proportional to reaction time, and it is therefore legitimate to take the loss during any convenient time as a measure of the rate constant. In all further experiments a period of 4 minutes was used, long enough to give an accurately weighable loss of metal, but not enough to change the diameter of the cylinder appreciably, or the amount of acid present.

FIG. 1.

Loss of weight of magnesium cylinders in acid solution at 25°.



1. 2 × 0·9 *cm.*, 2150 *r.p.m. in* 500 *c.c.* 0·1N-H_2SO_4.
2. 2 × 0·9 *cm.*, 1300 *r.p.m. in* 500 *c.c.* 0·1N-H_2SO_4.
3. 2 × 0·9 *cm.*, 1300 *r.p.m. in* 500 *c.c. acetate*-HCl *mixture* (pH = 1·09).
4. 3 × 0·9 *cm.*, 2150 *r.p.m. in* 400 *c.c.* 0·1N-*acetic acid.*

In order to extend the above procedure to the measurements of inhibiting power, a given cylinder, after duplicate runs in fresh portions of the acid solution, was again run twice in portions of acid to which the desired concentration of inhibitor had been added. The ratio

$$\frac{\text{Average loss in weight in solution with inhibitor}}{\text{Average loss of weight in pure acid solution}} \times 100$$

was termed the "relative corrosion," and was independent of actual loss of weight, which varied slightly from cylinder to cylinder since the dimensions were not all the same. The simple aliphatic amines are not very efficient inhibitors of the metal–acid reaction, and with magnesium and strong acids it was found that the main effect of adding the base was neutralisation. The reactions were therefore carried out in the sodium acetate-hydrochloric acid mixture referred to above. Large additions of amine could be made to it without sensible alteration of its pH of 1·09. Heterocyclic nitrogen compounds were much better inhibitors. Typical results are given in Table I, piperidine being the inhibitor.

TABLE I.

Acid: NaOAc–HCl mixture.
Time: 4 minutes.

Inhibitor: piperidine.
Temperature: 25°.

Concn. of inhibitor m.-mols./l.	Loss of wt. in acid (g. × 10^{-4}).			Loss of wt. in acid plus inhibitor (g. × 10^{-4}).			Relative corrosion.
5	216	210	Mean 213	185	181	Mean 183	88·8
10	199	197	198	162	161	161·5	82·0
15	196	201	198·5	154	148	151	76·0
20	198	202	200	140	144	142	71·0
30	202	204	203	129	125	127	62·5
40	198	205	201·5	107	112	109·5	54·1
60	197	202	199·5	90	93	91·5	48·9
80	200	204	202	85	81	83	41·2
100	204	199	202·5	70	75	72·5	36·0

RESULTS AND DISCUSSION.

Calculation of Rate Constants.—It has been stated (King and Schack, *loc. cit.*) that the rate of reaction is directly proportional to the velocity of the surface through the solution at speeds above 1000 cm./minute. Speeds used in this study were 1300 r.p.m. and 2150 r.p.m., giving for cylinders 0·9 cm. in diameter a linear velocity through the solution of 3675 and 6080 cm./minute, respectively. The ratio obtained by comparing the slopes of curves 1 and 2 in Fig. 1 shows that in the present case the rates are roughly, but not exactly, proportional to these velocities (ratio of speeds = 1·65; ratio of reaction velocities = 1·43). Kilpatrick and Rushton's relationship (*loc. cit.*), *i.e.*, reaction velocity proportional to (speed of rotation)$^{0·29}$, gives a calculated ratio of reaction velocities of 1·157, agreeing even less well. It was decided to use King and Schack's relationship in comparing the data of the present study with those of previous workers. The special first-order formula used in both the investigations just referred to was thus adjusted for speed of rotation and a constant k was calculated from the formula

$$k = \frac{2{\cdot}303V}{At} \cdot \log\frac{a}{(a-x)} \cdot \frac{1000}{L}$$

where V = volume of solution, in ml.; A = area of cylinder surface, in square cm.; t = time of run, in minutes; a = dissolving capacity of solution, in any units; x = amount dissolved, in the same units; L = linear speed of cylinder surface, in cm./minute.

TABLE II.

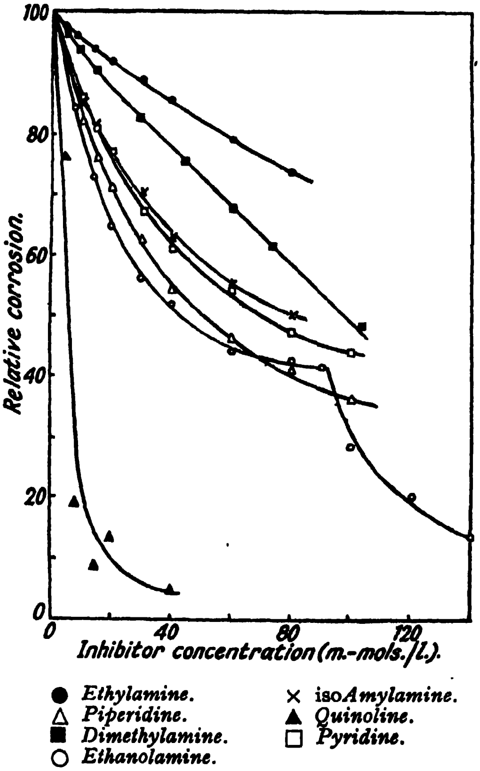
Corroding solution.		Linear speed, cm./min.	k.	Observers.*
H_2SO_4	0·05N	6080	0·205	H. and J.
,,	0·0575N	2000	0·229	K. and C.
,,	0·1N	6080	0·202	H. and J.
,,	0·1N	3675	0·242	,,
,,	0·15N	6080	0·201	,,
$CH_3{\cdot}CO_2H$	0·05N	6080	0·075	,,
,,	0·0597N	2000	0·090	K. and C.
HCl	0·05N	2000	0·248	,,
Acetate-HCl mixture (pH = 1·09)		3675	0·157	H. and J.
Pyridinium chloride (0·06M.) + pyridine (0·04M.)		2000	0·312	K. and C.
Pyridinium chloride (0·03M.) + pyridine (0·07M.)		2000	0·175	,,
Pyridinium sulphate (0·05M.) + pyridine (0·05M.)		6080	0·245	H. and J.

* K. and C. = King and Cathcart; H. and J. = present work.

This constant is then independent of volume used, concentration of acid, size of cylinder, and time of run, and reduces all results to a linear speed of 1000 cm./minutes. It has the dimensions cm./minute since the reaction is diffusion controlled. Table II gives the calculated values of k for various solutions used in the present work and also some recalculated from the work of King and Cathcart.

FIG. 2.

Relation between concentration and degree of inhibition in acetate–HCl *mixture at* 25°.



The table shows that the values obtained in the present work are of the same order as those obtained earlier and are in good agreement when direct comparison is possible, allowance being made for the fact that the constant is adjusted empirically for the difference in speed of rotation and is taken over only a short part of the reaction. The constant can be seen to vary with the acid used and is not directly related to the hydrogen-ion concentration. It is noteworthy that the pyridinium ion is an even more corrosive agent than the hydrogen ion and confirms the view that all the " acids " in the extended sense must be considered to take part in the reaction.

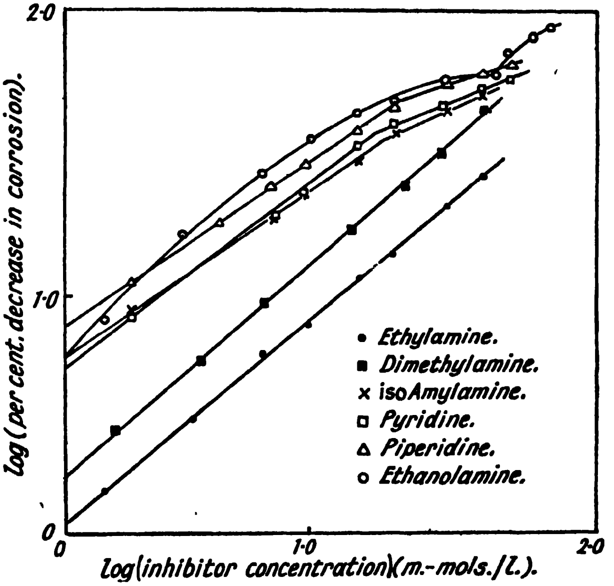
Effect of Inhibitors.—The figures for the inhibiting power of various amines in the acetate-acid mixture obtained as outlined in the experimental section are shown graphically in Fig. 2. Most of the curves are of the type to be expected if adsorption is the controlling process. The figure shows clearly the increased efficiency of inhibition due to: (*a*) increasing length of chain (compare ethylamine and *iso*amylamine), (*b*) multiplicity of chains (compare ethylamine and dimethylamine), (*c*) ring formation (compare *iso*amylamine and piperidine), (*d*) multiple rings (compare quinoline and piperidine).

These results extend to magnesium conclusions that have been reached after detailed observations of other metals (Mann, Lauer, and Hultin, *loc. cit.*) The curve for ethanolamine shows a remarkable and reproducible anomaly; this, and the greatly increased efficiency compared with the similar ethylamine, is probably due to solvation of the hydroxyl group, giving an enhanced blocking effect.

Erratic results were obtained with quinoline; an insoluble yellow complex was formed with magnesium salts giving an adherent coating so that this part of the work was discontinued.

If the results shown in Fig. 2 are plotted as log (% decrease in corrosion) against log (concentration of inhibitor), as in Fig. 3, it is clear that the relation log $I = \log a + b \log c$ (where I = % decrease in corrosion, c = inhibitor concentration) is valid up to about 40% decrease in corrosion for all inhibitors studied. For this part the slope (b) is about 0·75. With *iso*amylamine, pyridine, and piperidine there is a second straight part of the curve with a slope of about 0·40 (cf. Mann, Lauer, and Hultin, *loc. cit.*). If we assume that the inhibiting action is controlled by adsorption from the liquid on the solid metal, the values of b are of the right order. The break in the curve may be due to a change of packing necessary to accommodate the larger molecules, or to an overflow from primary to secondary cathodic areas according to Taylor and Rideal's theory ("Catalysis in Theory and Practice," 1922).

FIG. 3.



Temperature-coefficient Measurements.—Measurement of the rates of the inhibited and the uninhibited reactions were made over a range of temperature and the apparent energies of activation were calculated from the Arrhenius equation $k = Ae^{-E/RT}$.

The results given are the average of duplicate runs with each of four identical cylinders and are thus the mean of eight determinations. It has been shown (King and Cathcart, *loc. cit.*; King and Braverman, *J. Amer. Chem. Soc.*, 1932, **54**, 1744; King, *ibid.*, 1935, **57**, 828) that the observed energy of activation for the dissolution of metals by strongly acid solutions is probably, in fact, an energy of diffusion; the values found agree with that to be expected for a diffusion energy and are extremely low for a true activation energy. The mean energy of activation found in this study (3800 cals./g.-mol.) agrees with that found by other observers.

Whatever the mechanism, it is obvious from Table III that it is not inherently altered by the presence of inhibitors. Areas of surface are apparently blocked off, but the residual reaction is the same as before.

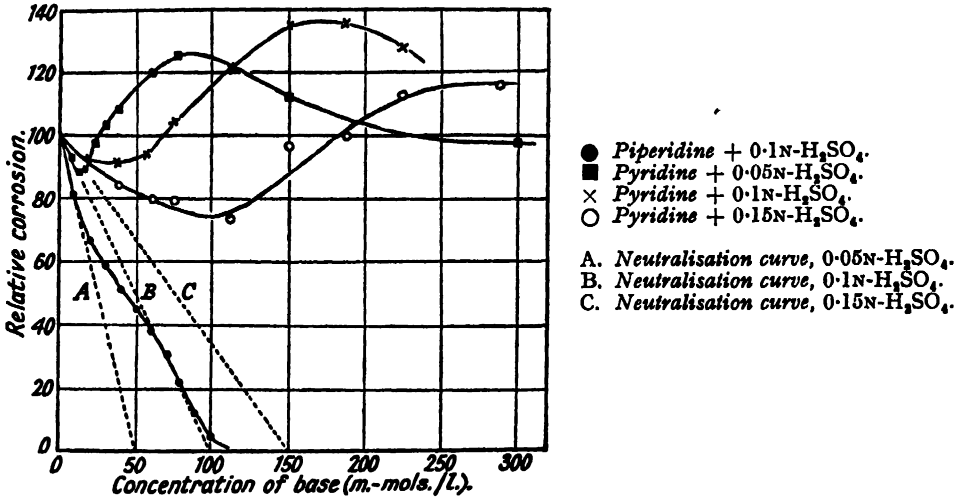
TABLE III.

Concn. of inhibitor (m.-mols./l.).	Loss of wt. (10^{-4}g.) at: 15°.	25°.	35°.	45°.	Energy of activation (cals./mol.): 25°/15°.	35°/25°.	45°/35°.	Mean.
0	158	199	245	296	3950	3790	3680	3800
20	—	154	197·5	248	—	4550	4450	4500
40	—	129·5	165	204	—	4460	4300	4380
60	—	107·5	135·5	167	—	4230	4170	4200
80	—	94	118	145	—	4160	4080	4120
100	—	84·5	105	128	—	3960	3820	3890

The apparent energy of activation is in all cases about 4000 cals./g.-mol. but shows a tendency to decrease with rise of temperature, for both the inhibited and the uninhibited reactions. There is also a sharp increase with the first increment of inhibitor, but with succeeding additions the energy decreases and approaches the value for the uninhibited reaction.

FIG. 4.

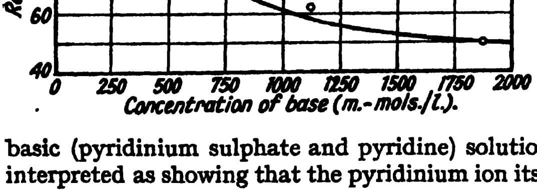
Effect of adding pyridine and piperidine to unbuffered acid solutions.



Experiments in Unbuffered Solutions.—As remarked earlier, the chief effect of adding a basic amine to an unbuffered solution of a strong acid is neutralisation. Thus the experimental curve for piperidine and sulphuric acid (Fig. 4) follows generally the theoretical curve for neutralisation. In the first part, however, the rate is always less than the theoretical, owing to the effect of the concurrent adsorption, but at the point of complete neutralisation, there is still a residual reaction equal to 4·6% of the original rate, showing that the piperidinium cation itself is acting as an " acid " in the extended sense.

FIG. 5.

Extended version of Fig. 4 for pyridine and 0·05N-sulphuric acid.



The experimental curves for pyridine show this effect even more clearly (also on Fig. 4). At the neutral points for three acid strengths it was found that the resulting pyridinium sulphate was more corrosive than the original sulphuric acid. Results obtained on adding extremely large amounts of pyridine to 0·05N-sulphuric acid are shown in Fig. 5.

Even when the solution was 1·8M. with respect to the pyridine, the reaction rate was still 50% of the uninhibited rate. Thus both faintly acid (pyridinium sulphate) and faintly basic (pyridinium sulphate and pyridine) solutions, show high reactivity, and this can only be interpreted as showing that the pyridinium ion itself is active in the metallic dissolution process. The curves of Fig. 4 and 5 therefore show the following effects: (*a*) initial neutralisation combined with slight inhibition, (*b*) a corrosive action by pyridinium ions which rises as the pyridinium ion/hydrogen ion ratio rises, (*c*) inhibition of pyridinium-ion corrosion by increasing amounts of pyridine. The complex nature of the interactions allows only general conclusions to be drawn and it is not yet possible to explain the shape of the curves in detail.

CANTERBURY UNIVERSITY COLLEGE,
CHRISTCHURCH, NEW ZEALAND.

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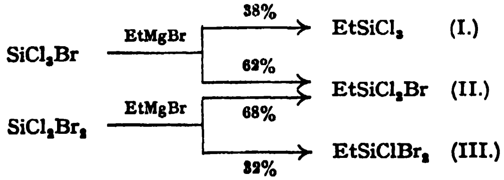
34. *Experiments on the Substitution Behaviour of the Silicon Chlorobromides.*

By C. J. Wilkins, N. P. H. Brown, and Alison D. Stevens.

Trichlorobromosilane and dichlorodibromosilane react with Grignard reagents with replacement of both chlorine and bromine, the proportion of bromine replaced being higher the larger the alkyl group. From the reactions of these silicon chlorobromides with ethylmagnesium bromide ethyldichlorobromosilane and ethylchlorodibromosilane have been isolated. Chlorotribromosilane and tetrabromosilane are unreactive towards Grignard reagents.

Although silicon tetrachloride reacts readily with alkylmagnesium bromides, experiments made in this laboratory by Lorking have shown that this reactivity does not extend to the tetrabromide, which indeed, fails to yield substitution products with methylmagnesium bromide at temperatures below 160°. Our results on the behaviour of the silicon chlorobromides towards Grignard reagents have shown that chlorotribromosilane resembles tetrabromosilane (silicon tetrabromide) in being unreactive; trichlorobromosilane and dichlorodibromosilane do, however, react. Both halogens undergo replacement, and with ethylmagnesium bromide the reactions proceed thus:



The percentages represent the atomic ratio of the two halogens from the silicon chlorobromide found in the precipitated magnesium halide from preparative experiments. Yields of the purified products (I), (II), and (III) were in similar proportions. The compounds, *ethyldichlorobromosilane* (II), b. p. 120—121°/768 mm., and *ethylchlorodibromosilane* (III), b. p. 141—143°/768 mm., are the first organo-substituted silicon chlorobromides to be reported. It has not proved possible to obtain the corresponding methyl compounds in a state of purity owing, it seems, to the proximities of the boiling points of the reactants and products.

In the series of tetrahalides examined the effect of the accumulation of bromine in reducing the reactivity not only of the bromine atoms themselves, but also of the adjacent chlorine, may well be connected with the steric influence of the rather large bromine atoms. Evidence for this view was obtained from an examination of the relative proportions of chlorine and bromine replaced from trichlorobromosilane and dichlorodibromosilane on their reaction with a series of Grignard reagents containing successively larger alkyl groups. It will be noticed from the following table that the larger the attacking group the higher the proportion of the larger halogen replaced.

Reagent.	MeMgBr.	EtMgBr.	Pr^{i}MgBr.	Bu^{t}MgCl.
Halide from SiCl$_3$Br, Cl, %	—	60	44	0
,, ,, Br, %	—	40	56	100
,, SiCl$_2$Br$_2$, Cl, %	52	39	5	—
,, ,, Br, %	48	61	95	—

These results, from experiments carried out on a small scale (0·01—0·02 g.-mol.) under comparable conditions, were again obtained by analysis of the precipitated magnesium halide. No attempt was made to isolate the volatile products from this series of reactions. Whilst high reproducibility could not be expected, the compositions of magnesium halide from the small-scale and preparative experiments using ethylmagnesium bromide are in reasonable accord.

Experimental.

Preparation of Silicon Chlorobromides.—Each of these three compounds was obtained from the reaction of silicon tetrabromide with the theoretical quantity of antimony trichloride (Schumb and Anderson, *J. Amer. Chem. Soc.*, 1937, **59**, 651). A mild reaction occurred on heating the mixture, and the product was tapped off at the appropriate temperature from the head of a 14-in. (Whitmore and Lux type) fractionating column packed with Fenske helices. After re-fractionation of the product yields were about 70%.

Silicon tetrabromide itself was obtained by passing bromine vapour over powdered silicon in a silica tube heated to redness. The product was left over mercury to remove free bromine, and distilled.

Reactions with Grignard Reagents.—In experiments conducted on a preparative scale the general procedure introduced by Kipping was followed. The reaction was carried out in an ice-cooled flask fitted with dropping funnel, stirrer, and reflux condenser. A solution of the Grignard reagent in ether was run slowly, with stirring, into the silicon chlorobromide diluted with 2—3 times its volume of ether. With trichlorobromosilane there was an immediate separation of magnesium halide, but dichlorodibromosilane was less reactive and the halide precipitate appeared only on heating the mixture under reflux. The magnesium halide was filtered off and extracted with ether, and the liquid fractionally distilled to remove ether and separate alkylated products.

In the reactions carried out on a small scale to establish the course of the substitution, equimolecular quantities of the reactants were heated under reflux until no more magnesium halide separated. The solution was then poured off, and the halide washed with hot ether and dissolved in water for analysis.

Analysis.—Chloride and bromide in admixture were determined by precipitation as silver halide, and a Mohr titration. In some instances bromide figures were checked by titration (in a separating funnel) with freshly standardised chlorine water, the titration being continued until the colour of bromine just failed to appear in successive small quantities of chloroform used as extractant. The silicon content of a compound was determined by hydrolysis in a platinum crucible containing water, followed by evaporation and ignition.

In certain cases determination of the strong acid liberated on hydrolysis sufficed to identify a compound.

The Products from Trichlorobromosilane and Ethylmagnesium Bromide.—The Grignard reagent (0·25 g.-mol.) was added to trichlorobromosilane (0·25 g.-mol.), and stirring was continued for half an hour whilst the mixture warmed to room temperature. Magnesium halide was removed and the ether distilled off. The residual liquid (about 30 c.c.) was decanted from a further small precipitate of magnesium halide, and carefully fractionated in an all-glass apparatus using the column mentioned above. The first distillation indicated the presence of components boiling in the vicinity of 80°, 100°, and 120°. Three systematic redistillations yielded about 1 c.c. of unreacted trichlorobromosilane (b. p. 80—82°), 5 c.c. of ethyltrichlorosilane (b. p. 99—102°), and 10 c.c. of *ethyldichlorobromosilane* (b. p. 120—121°) together with incompletely resolved intermediate fractions (Found, fraction b. p. 99—102°: Cl, 63·8; Br, 1·7%. Calc. for $EtSiCl_3$: Cl, 65·6%. Found, fraction b. p. 120—121°: Cl, 33·9; Br, 37·5; Si, 13·9%. $EtSiCl_2Br$ requires Cl, 34·1; Br, 38·4; Si, 13·5%).

The Products from Dichlorodibromosilane and Ethylmagnesium Bromide.—When equivalent quantities (0·4 g.-mol.) of the two reactants were mixed no reaction occurred in the cold, the Grignard reagent forming an oily lower layer. Magnesium halide separated during five hours' heating of the mixture under reflux, after which the products were isolated as before. There were obtained about 1 c.c. of unreacted dichlorodibromosilane (b. p. 105—107°), 14 c.c. of ethyldichlorobromosilane (b. p. 119·5—122°), and 4 c.c. of *ethylchlorodibromosilane* (b. p. 141—143°) (Found, fraction b. p. 119·5—122°: 0·0141 equiv. of acid per g. Calc. for $EtSiCl_2Br$: 0·0144. Found, fraction b. p. 141—143°: Cl, 13·8; Br, 61·4; Si, 11·3%. $EtSiClBr_2$ requires Cl, 14·1; Br, 63·3; Si, 11·1%.) It is suspected that the low figure for bromine in the analysis of the second ethyl compound may be due to slight further substitution of this halogen to give an impurity having similar volatility.

Attempted Methylation of Chlorotribromosilane.—The chlorobromide was heated under reflux for several hours with an ethereal solution of methylmagnesium bromide, but magnesium halide did not separate and two liquid layers remained. Next, the silicon halide and the solid Grignard reagent (0·33 g.-mol. of each) were heated at 120° for 10 hours; the recovered liquid, distilling at 125—135°, was essentially unreacted chlorotribromosilane (Found: 0·0134 equiv. of acid per g. Calc. for $SiClBr_3$: 0·0132; for $MeSiBr_3$, 0·0106; for $MeSiClBr_2$, 0·0126).

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CANTERBURY UNIVERSITY COLLEGE,
CHRISTCHURCH, NEW ZEALAND.

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35. *The Reaction of Bromine Trifluoride with Oxides and Some Oxy-acid Salts.*

By H. J. EMELÉUS and A. A. WOOLF.

The reaction of bromine trifluoride with twenty-eight oxides was studied. With CuO, B_2O_3, Tl_2O_3, SiO_2, GeO_2, TiO_2, As_2O_3, Sb_2O_3, SeO_2, UO_3, and I_2O_5 oxygen evolution was quantitative: in other cases a mixture of oxide and fluoride resulted. Metaphosphates were converted quantitatively into hexafluorophosphates, but orthophosphates gave a mixture of fluorophosphate and bromofluoride. An ionic reaction mechanism involving the "acid" $BrF_2^+PF_6^-$ is postulated to explain the formation of hexafluorophosphate. Orthoarsenates resembled orthophosphates. Potassium persulphate and pyrosulphate gave fluorosulphonate, whereas the pyrosulphite, thiosulphate, and sulphate gave equimolecular mixtures of fluorosulphonate and bromofluoride. Sodium dithionite and sulphite gave only bromofluoride. The relationship between the products and the anion structure is discussed. Oxygen was liberated quantitatively from iodates and bromates but incompletely from chlorates and carbonates.

QUALITATIVE observations on the reaction between bromine trifluoride and oxides were made by Ruff and his co-workers (*Z. anorg. Chem.*, 1931, **202**, 59; 1933, **214**, 91). Oxygen was found to be evolved, but a quantitative study of these reactions has shown that the reactivity of bromine trifluoride was over-emphasised, since for only twelve of the twenty-eight oxides examined was oxygen evolution complete. The reaction could not, therefore, be generally applied for the determination of oxygen in oxides. Certain of the quantitative reactions may, however, be of service in determining the heats of formation of bromine trifluoride and iodine pentafluoride. Thus in the case of silica the reaction is : $3SiO_2 + 4BrF_3 \longrightarrow 3SiF_4 + 3O_2 + 2Br_2$, all of the products being volatile. The same is true of arsenious oxide or the oxides of uranium. Similarly the reaction $6I_2O_5 + 20BrF_3 \longrightarrow 12IF_5 + 15O_2 + 10Br_2$, or the reaction with an iodate (see below) could be used in determining the heat of formation of iodine pentafluoride. The reaction of chlorine trifluoride with alkali-metal halides used by Schmitz and Schumacher (*Z. Naturforsch.*, 1947, **2a**, 362) to determine the heat of formation of chlorine trifluoride would not be applicable with bromine trifluoride or iodine pentafluoride because of the formation of complexes (Sharpe and Emeléus, *J.*, 1948, 2135). The criteria for ready reaction of an oxide with bromine trifluoride were that a volatile fluoride was produced, or that the fluoride formed was soluble in the reagent. Only in the reaction with vanadium pentoxide was an oxyfluoride formed; in the other cases, when attack was incomplete, the proportions of fluoride and unchanged oxide varied with the experimental conditions and had no special significance.

Salts of oxy-acids reacted readily with bromine trifluoride but the products depended on the nature of the anion. Potassium metaphosphate yielded the hexafluorophosphate, in which the co-ordination number of phosphorus was increased from four to six. The mechanism was probably ionic, the anion being first converted into phosphorus pentafluoride, which reacted in bromine trifluoride solution as $BrF_2^+PF_6^-$. This would resemble the acid $BrF_2^+SbF_6^-$ (Woolf and Emeléus, *J.*, 1949, 2865) and could undergo the neutralisation reaction, $K^+BrF_4^- + BrF_2^+PF_6^- \longrightarrow KPF_6 + 2BrF_3$. Indirect evidence for such a mechanism was provided by the fact that bismuth orthophosphate was converted by bromine trifluoride into bismuth trifluoride with complete elimination of phosphorus and oxygen. This was due to the insolubility of the bismuth fluoride in the solvent which prevented an ionic reaction with the unstable intermediate $BrF_2^+PF_6^-$. The formation of hexafluorophosphates by the reaction of metallic halides and a small excess of phosphorus pentachloride may be explained in the same way. The dry reaction between excess of potassium or sodium fluoride and phosphorus pentachloride which produces hexafluorophosphates in much lower yields (Lange, *Ber.*, 1932, **65**, 1253) probably follows an essentially different course. Orthophosphates of metals which form bromofluorides also yielded hexafluorophosphates, but the product contained unchanged bromofluoride. Sodium orthophosphate, for example, gave two molecular proportions of sodium bromofluoride and one of sodium hexafluorophosphate. Sodium bromofluoride is relatively unstable and the analytical results showed a deficit of bromine trifluoride in the product. These reactions can also occur by an ionic mechanism, the products depending on the cation : phosphorus ratio. Pyrophosphates of univalent cations, for example, should give equimolecular proportions of bromofluorides and fluorophosphates. Silver orthoarsenate gave a similar result to sodium orthophosphate, the arsenic appearing in the product as silver hexafluoroarsenate with two molecular proportions of the stable silver bromofluoride.

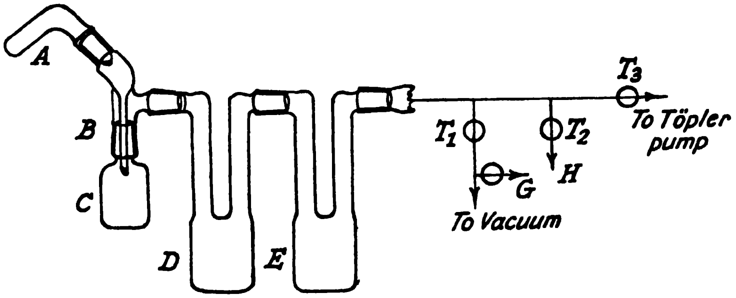
Salts of the sulphur oxy-acids reacted with bromine trifluoride in a way which was related directly to the anion structure. Potassium persulphate and pyrosulphate gave potassium fluorosulphonate, whereas potassium pyrosulphite, thiosulphate, and sulphate all gave equimolecular mixtures of the fluorosulphonate and potassium bromofluoride. The structures of these anions are known and in the case of both persulphate and pyrosulphate two S–O bonds are broken, oxygen in excess of that required to produce the SO_3F ion being eliminated. The oxygen evolution was not studied quantitatively, but it is unlikely that fluorine or bromine oxides were formed. In the bivalent pyrosulphite, thiosulphate, and sulphate ions the structures allow only one SO_3F ion to be formed and consequently one of the univalent cations was converted into the bromofluoride. The four-fold co-ordination round sulphur is retained because in an anion formed with oxygen or fluorine spatial considerations prevent a higher value being attained (Pauling, *J. Amer. Chem. Soc.*, 1933, **55**, 1895; 1927, **49**, 765). It is interesting that the pyramidal sulphite ion in sodium sulphite formed sodium bromofluoride and not sodium fluorosulphonate. Sodium dithionite also gave sodium bromofluoride as the only product. This evidence excludes the structure $[O_3S{-}S{\rightarrow}O]^{2-}$ proposed by Deines and Elstner (*Z. anorg. Chem.*, 1930, **191**, 340), since this would have given fluorosulphonate. It does not however distinguish between the structures $[O_2S{-}SO_2]^{2-}$ and $[O_2S{-}O{-}S{\rightarrow}O]^{2-}$, either of which could give bromofluoride.

EXPERIMENTAL.

Bromine trifluoride was prepared and purified as already described (Sharpe and Emeléus, *J.*, 1948, 2135). The oxides and salts used were whenever possible of AnalaR quality. The majority of the experiments were done in the apparatus shown in the figure, which was constructed of Pyrex glass except for the transparent silica reaction vessel *C*.

Tube *A* contained the bromine trifluoride and, together with the flask *C*, which held a weighed amount of oxide (or salt), was attached by standard ground joints to the dropping-tube *B*. Traps *D* and *E* were cooled in liquid air, and connections were made to the vacuum and Töpler pumps as shown.

Approx. 1—2 c.c. of freshly distilled bromine trifluoride were poured into *A*, which was then cooled in liquid air. Sufficient oxide to produce 50—70 c.c. of oxygen was weighed into *C* through a long funnel. While *A* was cooled and tap T_3 closed, the apparatus was evacuated slowly with T_1 and T_2 open. Traps *D* and *E* were cooled in liquid air, and *A* was allowed to reach room temperature for a short time, whereupon traces of volatile impurities in the bromine trifluoride distilled into *D*. Taps T_1 and T_3 were then closed and a known volume of pure nitrogen (*ca.* 25—30 c.c.) was passed into the reaction system from the calibrated manometer, *H*, by opening T_2; this served to prevent rapid distillation of bromine trifluoride into the cooled trap. The difference in level between *G* and *H* was observed, *C* was cooled in liquid air, and a few drops of liquid bromine trifluoride were introduced by rotating the tube *A* and partly melting its contents. The vessel *C* was warmed to initiate reaction, and further additions of bromine trifluoride were made in the same way, the completion of reaction being indicated by the manometer level. Some reactions occurred at room temperature, others required heat, and the remainder were incomplete after refluxing the oxide with liquid bromine trifluoride for periods up to 2 hours. It was essential to avoid contact of bromine trifluoride with the silicone grease used to lubricate the ground joints.



The oxygen–nitrogen mixture was drawn off with the Töpler pump and measured, excess of bromine trifluoride distilling from *C* to *D* during the process. The residue in *C* was weighed, and the equivalent weight of the reaction product was thereby determined.

Reaction of Bromine Trifluoride with Oxides.—The oxides from which a quantitative oxygen evolution was observed were: CuO, B_2O_3, Tl_2O_3, SiO_2, GeO_2, TiO_2, As_2O_3, Sb_2O_3, SeO_2, UO_3, I_2O_5. In the case of CuO, the product was CuF_2. B_2O_3, Tl_2O_3, SiO_2, GeO_2 and TiO_2 gave BF_3, TlF_3, SiF_4, GeF_4, and TiF_4 respectively. As_2O_3 and Sb_2O_3 were converted into AsF_5 and $SbBrF_8$. SeO_2 and UO_3 gave SeF_6 and UF_6, while I_2O_5 was converted into IF_5.

For the following oxides attack by bromine trifluoride was incomplete under the conditions used: BeO, MgO, ZnO, CdO, HgO, CaO,Al_2O_3, CeO_2, SnO_2, PbO, PbO_2, ZrO_2, ThO_2, MnO_2, Fe_2O_3. The product was a mixture of metal fluoride and oxide. V_2O_5 was converted into VOF_3, and BiOCl into BiF_3.

Reaction of Bromine Trifluoride with Phosphates and Arsenates.—Potassium metaphosphate was prepared by heating AnalaR potassium dihydrogen phosphate at 600° (Found: KPO_3/KH_2PO_4, 0·866. Calc.: 0·868). About 0·7 g. was refluxed with 10 c.c. of bromine trifluoride without dissolution occurring. The solid residue after removal of excess of reagent was soluble in cold water and gave no precipitate with silver nitrate; bromide and phosphate were thus absent. The hexafluorophosphate ion was determined as the nitron salt (Lange, *Ber.*, 1928, **30**, 799) (Found: PF_6, 79·2%; equiv., 182. Calc. for KPF_6: PF_6, 78·8%; equiv., 184. Found, for the nitron salt: C, 52·3; H, 4·0; N, 12·1. Calc. for $C_{20}H_{16}N_4,HPF_6$: C, 52·4; H, 3·7; N, 12·2%). For preparation of larger quantities of potassium hexafluorophosphate by this method, 5 g. of salt were obtained conveniently from 10 c.c. of reagent. Sodium metaphosphate reacted similarly, yielding the hexafluorophosphate (Found: PF_6, 85·6%; equiv., 165. Calc. for $NaPF_6$: PF_6, 86·2%; equiv., 166. Found, for the nitron salt: C, 52·3; H, 3·7; N, 12·0%).

Anhydrous sodium orthophosphate, made from AnalaR disodium hydrogen phosphate and excess of sodium hydroxide and dried at 400°, was insoluble in boiling bromine trifluoride. On evaporation of the latter in a vacuum, the residue was a mixture of sodium fluorophosphate and impure sodium bromofluoride in a 1 : 2 molecular ratio. The product was decomposed with dilute nitric and sulphurous acids in a stoppered bottle, and the bromine precipitated as silver bromide. Fluorophosphate was determined as the nitron salt, after the aqueous solution had been boiled with dilute acetic acid to remove hydrobromic acid formed in the decomposition. It was shown that nitron acetate gave no precipitate with M/6-potassium bromate. The comparative stability of hexafluorophosphate to hydrolysis by dilute sodium carbonate solution enabled the fluorine present as bromofluoride to be separately determined after hydrolysis of the mixture with this reagent [Found: Na, 14·0; Br, 29·9; PF_6, 30·5; F (as BrF_4), 31·6. Calc. for $NaPF_6 + 2NaF,0{\cdot}91BrF_3$: Na, 13·9; Br, 29·3; PF_6, 29·1; F(as BrF_4), 28·5%]. The high value found for fluorine is due to partial decomposition of the hexafluorophosphate. In a blank experiment 8·2% of the total fluorine in KPF_6 was hydrolised.

Bismuth orthophosphate, prepared by double decomposition of dilute nitric acid solutions of bismuth nitrate and sodium phosphate, gave the trifluoride as the only product of reaction with bromine trifluoride, the residue being free from bromine and phosphate. Fluorine was determined by fusion with sodium carbonate, extraction of sodium fluoride with water, and precipitation as calcium fluoride (Found: F, 21·7%; equiv., 263. Calc. for BiF_3: F, 21·4%; equiv., 266). The oxygen evolved in the reaction was collected and measured, and corresponded to 106% of the theoretical value.

Silver orthoarsenate, prepared by double decomposition, was dried at 250° (Found: Ag, 69·7. Calc. for Ag_3AsO_4: Ag, 69·9%). Reaction with excess of bromine trifluoride gave a clear solution from which excess of reagent was evaporated in a vacuum in the usual way. The residue gave a nitron precipitate and contained bromine and arsenic. The fluorine was determined as in the case of the product from sodium orthophosphate, silver hexafluoroarsenate being decomposed only slowly by sodium carbonate solution [Found: Ag, 40·0; Br, 19·5; F (as BrF_4), 20·0%; equiv., 822. Calc. for $AgAsF_6 + 2AgBrF_4$: Ag, 39·3; Br, 19·4; F (as BrF_4), 18·5%; equiv., 825].

Reaction of Bromine Trifluoride with Metallic Halides and Phosphorus Pentachloride.—In preliminary experiments it was found that the product from potassium chloride and a small excess of phosphorus pentachloride was a mixture containing about 46% of hexafluorophosphate, the remainder being potassium bromofluoride. Silver chloride gave a similar result. Using pentabromide in place of pentachloride the yields of hexafluorophosphate were quantitative. These and certain related reactions are being more fully studied.

Reaction of Bromine Trifluoride with Salts of Sulphur Oxy-acids.—The reaction product from potassium persulphate was analysed by decomposition with boiling alkali for the fluorine determination. Fluorine was precipitated and weighed as calcium fluoride and then converted into sulphate to provide a correction for co-precipitated calcium sulphate. The sulphate formed on acid hydrolysis was precipitated with barium chloride, and fluorosulphonate was determined as the nitron salt (Traube, *Ber.*, 1919, **52**, 1272) (Found: S, 23·3; F, 12·7; SO_3F, 72·7%; equiv., 279. Calc. for $2KSO_3F$: S, 23·4; F, 13·8; SO_3F, 71·7%; equiv., 276). The nitron salt was also analysed (Found: C, 58·2; H, 4·1; N, 13·2. Calc. for $C_{20}H_{16}N_4HSO_3F$: C, 58·2; H, 4·1; N, 13·6%). The product from potassium pyrosulphate was analysed for potassium by conversion into sulphate and for fluorosulphonate as above (Found: K, 27·5; SO_3F, 72·3. Calc. for KSO_3F: K, 28·3; SO_3F, 71·7%. Found, for the nitron salt: C, 58·2; H, 4·4; N, 13·1%).

Potassium pyrosulphite gave a mixture consisting of an equimolecular mixture of potassium bromofluoride and potassium fluorosulphonate. Bromine was determined as silver bromide after decomposition with sulphurous acid in a stoppered bottle. Fluorosulphonate was determined as the nitron salt by the same procedure as for the determination of hexafluorophosphate in presence of bromofluoride. The high result was probably due to co-precipitation of nitron hydrobromide. Sulphur was determined as barium sulphate, after reduction of the aqueous solution of product with hydrazine hydrate, decomposition of the fluorosulphonate with hydrochloric acid, and a final heating at 100° for 24 hours to remove hydrogen bromide and fluoride (Found: Br, 23·8; SO_3F, 32·0; S, 9·7%; equiv., 334. Calc. for $KBrF_4 + KSO_3F$: Br, 24·0; SO_3F, 29·6; S, 9·6%; equiv., 333).

Potassium thiosulphate was dried at 150° before use (Found: S_2O_3, 58·7. Calc. for $K_2S_2O_3$: 58·9%). The product of reaction with bromine trifluoride was an equimolecular mixture of potassium bromofluoride and fluorosulphonate (Found: K, 22·8; Br, 23·1; S, 11·2; F, as BrF_4, 22·4%; equiv., 329. Calc. for $KBrF_4 + KSO_3F$: K, 23·5; Br, 24·0; S, 9·6; F, as BrF_4, 22·8%; equiv., 333). The bromofluoride was decomposed by sodium carbonate solution without appreciable decomposition of the fluorosulphonate. Potassium sulphate gave the same product (Found: Br, 24·1%; equiv., 331. Calc. for $KSO_3F + KBrF_4$: Br, 24·0%; equiv., 333). The product from silver sulphate was similar (Found: Ag, 46·7; Br, 17·4; S, 7·2%; equiv., 468. Calc. for $AgSO_3F + AgBrF_4$: Ag, 45·9; Br, 17·1; S, 6·8%; equiv., 470).

Sodium dithionite on treatment with bromine trifluoride gave sodium bromofluoride as the only solid product (Found: Na, 13·0; Br, 44·1; F, 40·6. Calc. for $NaBrF_4$: Na, 12·9; Br, 44·7; F, 42·4%). The material used was only 85% pure with respect to the dithionite ion. The latter was determined by its reduction of ammoniacal silver nitrate to silver, which was converted into the bromide after filtration and dissolution in nitric acid. Sodium was determined as sulphate (Found: Na, 29·6. Calc. for $Na_2S_2O_4$: 26·4%), the high value being probably due to the presence of sodium sulphite and sodium chloride, the latter being used as a salting-out agent in manufacture. All of the sodium in the impure dithionite was converted into bromofluoride (Found: equiv., 408. Calc. for $NaBrF_4$ on the 29·6%-Na figure: equiv., 401). Sodium sulphite also gave the bromofluoride on reaction with bromine trifluoride, the product being free from sulphur (Found: Na, 13·7; Br, 44·1. Calc. for $NaF,0{\cdot}92BrF_3$: Na, 13·5; Br, 45·1%).

Qualitative Examination by X-Ray Powder Photography of the Reaction Products from Salts of Sulphur Oxy-acids.—Specimens were sealed in Pyrex capillaries and exposed to copper $K\alpha$ radiation for approximately equal times, the filament current and voltage of the *X*-ray tube being maintained at constant values. The resulting films were compared by superposition. It was found that the lines obtained from the products from potassium persulphate and persulphate (Group A) were identical as regards position and relative intensity, the latter being judged visually. Those of the products from potassium thiosulphate, pyrosulphite, and sulphate (Group B) were also identical. A specimen of potassium bromofluoride was prepared from potassium chloride, and all of the lines of this compound were identified in the photographs from Group B, though all were absent in the photographs from Group A. The bromofluorides obtained from sodium carbonate and dithionite gave identical photographs.

Reaction of Bromine Trifluoride with Halogenates.—With potassium iodate the oxygen evolution was 97 and 101% of theory in duplicate experiments. The solid product was potassium bromofluoride (Found: K, 20·7; Br, 40·4; F, 38·2%; equiv., 197. Calc. for $KBrF_4$: K, 20·0; Br, 41·0; F, 39·0%; equiv., 195). Mercurous iodate, prepared by double decomposition of potassium iodate and mercurous nitrate in dilute nitric acid solution and dried at 120°, gave 100% oxygen evolution. The solid product was mercuric fluoride (Found: Hg, 83·2; F, 15·2%; equiv., 234. Calc. for HgF_2: Hg, 84·0; F, 16·0%; equiv., 238). Thallous iodate gave an oxygen evolution of 104%. The white residue of thallic fluoride (Found: Tl, 77·9; F, 21·9%; equiv., 271. Calc. for TlF_3: Tl, 78·3; F, 21·8%; equiv., 261) left on removal of excess of bromine trifluoride became brown in moist air and was decomposed by water to thallic hydroxide; when dried at 120° it gave the trioxide (Found: Tl, 88·4. Calc. for Tl_2O_3: 89·5%). This confirms the observation of Hannebohn and Klemm (*Z. anorg. Chem.*, 1936, **229**, 337) who prepared thallic fluoride by the action of fluorine on the oxide.

Bromine trifluoride liberated oxygen quantitatively from manganese iodate. The product was a mixture of the bi- and the tri-fluoride together with a small proportion of combined bromine trifluoride. A typical composition was: MnF_2, 37; MnF_3, 63; BrF_3, 5. Lead iodate gave a mixture of plumbous and plumbic fluorides free from other halides and containing in successive experiments 33 and 39% of PbF_4. Cobaltous iodate similarly lost all its oxygen and gave a mixture of 64% of CoF_3 and 36% of CoF_2. In the reaction with potassium bromate the evolution of oxygen was measured and found to be complete. For potassium chlorate, however, only one third was evolved as such. The solid residue in each case was potassium bromofluoride and it is possible that the chlorate yielded chlorine dioxide or even chlorine dioxyfluoride (Schmitz and Schumacher, *Z. anorg. Chem.*, 1942, **249**, 238). The reaction between bromine trifluoride and carbonates appears from preliminary experiments to be similar, since only one-third of the oxygen was liberated as molecular oxygen. The solid products from lithium and beryllium carbonate were reagent-insoluble fluorides contaminated with a trace of solvent (Found: Li, 23·2%; equiv., 59·9. Calc. for $2LiF,0{\cdot}03BrF_3$: Li, 23·3%; equiv., 59·9) (Found: Br, 8·1; F, 74·2. Calc. for $BeF_2,0{\cdot}06BrF_3$: Br, 8·7; F, 75·0%). Sodium carbonate, however, was soluble and the bromofluoride resulted (Found: Br, 43·1; F, 42·3%; equiv., 175. Calc. for $NaBrF_4$: Br, 44·7; F, 42·4%; equiv., 179).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 9th*, 1949.]

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36. *Afzelin (Kœmpferol-3-rhamnoside), a New Glycoside isolated from Doussié.*

By F. E. KING and R. M. ACHESON.

The principal constituent of a powdery material occluded in a sample of doussié, a timber derived from trees of the genus *Afzelia*, is *kæmpferol*-3-*rhamnoside*, a new glycoside to which the name *afzelin* has been given.

THE conversion of a log of doussié, the timber of various species of *Afzelia*, revealed a "shake" filled with a pale brownish-yellow powder. Part of the log including the shake was submitted to the Director of the Forest Products Research Laboratory, Department of Scientific and Industrial Research, and we are indebted to Mr. W. G. Campbell of that Laboratory for a supply of the substance and for the following note on its occurrence. "Type specimens of the wood of *Afzelia* spp. commonly show a yellow deposit in some of the pores. The large deposit in the specimen under consideration probably arose as a result of the evaporation of water from tree sap which had oozed into a large fissure or 'shake.' Shakes are caused by various agencies such as, for example, internal stresses in the standing trees, damage by lightning or by impact with other trees during felling operations."

No clue as to the composition of the powder was to be found in the literature, which is without reference to any chemical investigation of the *Afzelia* genus, but from its solubility in water and the formation of a voluminous micro-crystalline precipitate on heating with aqueous acid, the presence of a glycoside was inferred. Further investigation revealed that apart from small quantities of two unidentified substances, the principal constituent is the formerly unknown *kæmpferol*-3-*rhamnoside*, for which we propose the name *afzelin*.

Several kæmpferol glycosides have been described which afford rhamnose on hydrolysis (see "The Chemistry of Natural Colouring Matters," Mayer-Cook, 1943, pp. 182, 183). One of these, robinin, is of interest in that on enzymic hydrolysis (Zemplen and Bognar, *Ber.*, 1941, **74**, 1783), kæmpferol-7-rhamnoside is obtained, apparently the only kæmpferol monorhamnoside hitherto definitely characterised. Of the others, in only three, *viz.*, kæmpferitrin, lespedin, and an unnamed compound found in the flowers of Australian acacia species by Petrie (*Biochem. J.*, 1924, **18**, 957), is rhamnose the sole glycosidic component. Although the nature of its hydrolysis products was clearly established, little more is known of the acacia colouring matter and nothing appears to have been done to characterise the glycoside or determine its composition. Lespedin, on the other hand, has been fully identified, and its constitution was shown by the usual chemical methods to be kæmpferol-3 : 7-dirhamnoside (Hattori and Hasegawa, *Proc. Imp. Acad. Japan*, 1940, **16**, 9; Hasegawa, *Acta Phytochim.*, 1940, **11**, 299). Kæmpferitrin, the yellow pigment of *Indigofera arrecta*, also gives two molecules of rhamnose when hydrolysed (A. G. Perkin, *J.*, 1907, **91**, 435), but there is no chemical evidence to show the position of the sugar residues. On the supposition that those flavonol glycosides which differ appreciably in their ultra-violet absorption from the corresponding aglycones are 3-glycosides, Tasaki (*Acta Phytochim.*, 1925, **2**, 119, 129) has classified kæmpferitrin as a 3-bioside, but it is evident that the argument cannot be exclusive of a 3 : *x*-dimonoside structure. Moreover, the close resemblance observed by Tasaki between the spectra of quercetin and rutin, of which the latter was later shown by Attree and A. G. Perkin (*J.*, 1927, 234) to be quercetin-3-rutinoside, weakens any conclusions which may be drawn from these measurements.

Of the crude material collected from the afzelia " shake " some 20 g. were available for investigation. Hydrolysis of a portion with 2% sulphuric acid precipitated an aglycone which was undoubtedly kæmpferol (5 : 7 : 4′-trihydroxyflavonol), but a persistent impurity depressed its m. p. to 273—275°. The glycoside was therefore dissolved in aqueous ethanol, and tannins, etc., were precipitated with lead acetate. After removal of excess of lead as sulphide, the solution was evaporated, and the residue subjected to fractional crystallisation from water. The principal fraction consisted of the yellow crystalline afzelin, having the ferric chloride reaction and strong blue-green fluorescence in sulphuric acid characteristic of kæmpferol.

Hydrolysis of the purified glycoside liberated kæmpferol, m. p. 279°, identical with an authentic specimen of the flavonol kindly provided by Professor W. Bradley, Leeds University. From the filtrate neutralised with barium carbonate, phenylhydrazine acetate precipitated an osazone shown by direct comparison to be L-rhamnose osazone, m. p. 180—181°.

The position of the sugar residue was determined by methylation with excess of diazomethane and acid hydrolysis of the glassy product, whereby a crystalline *O*-trimethylkæmpferol was obtained having the properties of 5 : 7 : 4′-trimethoxyflavonol previously synthesised by Kostanecki, Lampe, and Tambor (*Ber.*, 1904, **37**, 2098). A determination of the ultra-violet absorption of the glycoside in methanol gave $\lambda\lambda_{\text{max.}}$ 2650, 3450 A.; $\lambda_{\text{min.}}$ 2810 A.; log $\varepsilon_{\text{max.}}$ 4·39, 4·12, and log $\varepsilon_{\text{min.}}$ 4·08, respectively, in fairly close agreement with $\lambda\lambda_{\text{max.}}$ 2675, 3700 A., and log $\varepsilon_{\text{max.}}$ 4·12, 4·28, for kæmpferol (Skarzynski, *Biochem. Z.*, 1939, **301**, 150). In its lack of a maximum at 3100 A. characteristic of kæmpferol and of flavonols in general unsubstituted in the 3-position (see Skarzynski, *loc. cit.*), afzelin thus conforms to Tasaki's classification.

From the solution obtained by extracting crude afzelin with a limited quantity of boiling water a colourless crystalline *compound*, $C_{15}H_{12}O_6$, was isolated. Its properties suggest that it has a tetrahydroxydihydroflavone structure, but the amount available did not admit of its full identification. The third substance encountered has not been obtained in a homogeneous condition.

EXPERIMENTAL.

Isolation of Afzelin.—The light powdery solid (8·6 g.) from the afzelin shake was dissolved in warm aqueous ethanol (250 c.c.; 40%). After being filtered from wood fragments, etc., the yellow solution was treated with aqueous lead acetate (100 c.c.; 10%) until no further immediate precipitation took place (the use of basic lead acetate caused precipitation of almost all the dissolved material). The product was then centrifuged, and the filtrate saturated with hydrogen sulphide to precipitate the residual lead, after which the solution was evaporated under reduced pressure to 150 c.c. A yellow precipitate (A) (1·95 g.), m. p. 155—160°, was formed after 24 hours at 0°. The filtrate from this was further concentrated (to 80 ml.) and when left at 0° for several days gave a second yellow precipitate (B) (4·1 g.), m. p. 158—165°. Little material remained in the solution, which was then discarded.

Product (A) was treated with boiling water (55 c.c.), thereby leaving a residue consisting of fairly pure afzelin. On cooling to room temperature, the filtrate deposited a very pale yellow solid (0·4 g.), later proved to be a new compound $C_{15}H_{12}O_6$ (*q.v.*). When this had been removed, a further deposition of afzelin (0·62 g.) occurred gradually at 0°. The precipitate was collected, and the filtrate, diluted to 150 c.c., was heated to boiling with product (B). Again the undissolved solid consisted of afzelin, and a further quantity (0·85 g.) crystallised at room temperature. Cooling to 0° caused the appearance of a solid (2·4 g.), which on recrystallisation was separated into afzelin (0·5 g.), and a yellow substance (1·9 g.), m. p. 208—212° (sintering at 150°); unlike the other two products isolated, it gave in ethanol solution a yellow ferric reaction. This impure product was not further examined.

The glycoside *afzelin* crystallised from water–ethanol (4 : 1) as a hydrate consisting of yellow prisms, m. p. 172—174° (effervescence) (Found : C, 54·7, 55·1; H, 5·3, 5·3. $C_{21}H_{20}O_{10},1\frac{1}{2}H_2O$ requires C, 54·9; H, 5·0. Found, after drying at 125—130° in a vacuum : C, 57·8, 57·3; H, 5·2, 5·1; loss, 6·2. $C_{21}H_{20}O_{10}$ requires C, 58·3; H, 4·6; loss, 5·9%). A Zeisel determination showed the absence of methoxyl groups. It dissolved readily in alcohols and moderately in ether. Reduction with magnesium in alcoholic hydrochloric acid gave a red colour identical with that obtained from kæmpferol under the same conditions. Treatment with concentrated sulphuric acid changed the colour of the glycoside to orange, and it then dissolved to a yellow-green solution with an intense green-blue fluorescence; heating, which changed the colour to brown, finally caused charring. The addition of basic lead acetate to an aqueous alcoholic solution of the glycoside gave a yellow-green precipitate, but dilute lead acetate produced only an opalescence.

Hydrolysis of Afzelin.—The anhydrous glycoside (0·2002 g.) dissolved easily in hot aqueous 2% sulphuric acid (25 ml.). When the solution was refluxed for 1 hour a yellow precipitate was formed, which was collected next day, the filtrate and washings being retained.

The dried aglucone weighed 0·1324 g. (99·8% calculated on the basis of one rhamnose unit per molecule). It separated from glacial acetic acid in yellow prisms, m. p. 279°, alone or mixed with an authentic specimen of kæmpferol, m. p. 279° (Found, after drying at 110° in a vacuum: C, 62·7; H, 3·8. Calc. for $C_{15}H_{10}O_6$: C, 62·9; H, 3·5%).

The solution and washings from which the aglucone had been collected were heated on a steam-bath and neutralised with barium carbonate. After removal of the precipitated sulphate the liquid was evaporated, giving a brownish gum (0·0833 g.), which was dissolved in hot water (8 c.c.). A test portion of the solution reduced hot, but not cold, Fehling's solution. Aqueous phenylhydrazine acetate (0·4 c.c. of a mixture containing 10 c.c. of phenylhydrazine and 10 c.c. of acetic acid diluted to 25 ml. with water) was added, and after 10 minutes at 100° a precipitate formed (required for the formation of rhamnose osazone, 9 minutes). One hour later the mixture was cooled, and the osazone collected. Its crystalline form was identical with that of a specimen similarly prepared from L-rhamnose, and after crystallisation from ethanol it had m. p. and mixed m. p. 180—181° to a deep red liquid (Found: C, 62·3; H, 6·5. Calc. for $C_{18}H_{22}O_3N_4$: C, 63·1; H, 6·4%).

Methylation of Afzelin.—The glycoside (0·3 g.) in methanol solution (20 ml.) was repeatedly treated with ethereal diazomethane until the solution no longer gave a green colour with alcoholic ferric chloride. The pale brown gum obtained after removal of the solvent could not be induced to crystallise; it was therefore hydrolysed by boiling for 2 hours with 2% sulphuric acid (35 c.c.). Next day, the precipitate was collected, and after 3 crystallisations from aqueous ethanol it formed very pale yellow needles, m. p. 151° (Found: C, 62·6; H, 5·5. Calc. for $C_{18}H_{16}O_6,H_2O$: C, 62·4; H, 5·2. Found, after drying at 135° in a vacuum: C, 65·4; H, 5·1; loss, 5·6. Calc. for $C_{18}H_{16}O_6$: C, 65·85; H, 4·9; loss, 5·2%). The compound was evidently 3-hydroxy-5 : 7 : 4′-trimethoxyflavone, m. p. 151—152°, synthesised by Kostanecki, Lampe, and Tambor (*loc. cit.*), and gave identical reactions with dilute sodium hydroxide and concentrated sulphuric acid, and a dull reddish-black colour with ferric chloride in ethanol.

The Compound $C_{15}H_{12}O_6$.—The pale yellow solid (0·4 g.) obtained in the course of purifying afzelin dissolved completely in boiling water (33 c.c.) and on cooling crystallised in colourless needles. After two further crystallisations it melted at 225—227° to a deep-red liquid, after becoming yellow at 200° (Found: C, 55·6, 55·1; H, 5·0, 5·0. $C_{15}H_{12}O_6,2H_2O$ requires C, 55·6; H, 4·9. Found, after drying at 110° in vacuum: C, 62·2, 62·7; H, 4·3, 4·5; loss 10·7. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2; loss, 11·1. Ultra-violet light absorption in methanol $\lambda_{max.}$ 2900 A., log $\varepsilon_{max.} = 4·24$; $\lambda_{min.}$ 2510 A., log $\varepsilon_{min.} = 3·37$; inflection at *ca.* 3270 A.). It contained no methoxyl groups. It dissolved very easily in ethanol, and the solution gave a dull red ferric colour. The *compound* was stable to boiling 2% aqueous sulphuric acid. It dissolved in the cold concentrated acid to a yellow solution devoid of fluorescence even under ultra-violet light. The colour was discharged by a trace of concentrated nitric acid; on heating it became red and finally darkened from charring. The compound reacted immediately with bromine in acetic acid, and dissolved in aqueous sodium hydrogen carbonate (3%) to a very pale yellow solution. Addition of sodium hydroxide deepened the colour, and the addition of acid regenerated the compound unchanged. It slowly reacted with alcoholic 2 : 4-dinitrophenylhydrazine to give a crystalline precipitate; reduction with magnesium in ethanolic hydrochloric acid gave a pink colour, lighter than that similarly obtained from kæmpferol or afzelin. A derivative separating from ethanol in colourless needles, m. p. 160—164°, was obtained by the action of boiling acetic anhydride and pyridine, but the amount was too small for purification.

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37. *Fluorescent Reagents. Acyl Chlorides and Acyl Hydrazides.*

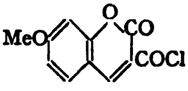
By WILSON BAKER, C. N. HAKSAR, and J. F. W. MCOMIE.

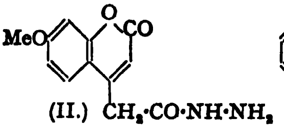
The paper describes some fluorescent acyl chlorides and hydrazides derived from coumarin-carboxylic acids, and a number of their derivatives formed by reaction with alcohols, amines, and carbonyl compounds. The fluorescence of these derivatives is designed to aid their separation by chromatographic methods. The two best reagents are 7-methoxycoumarin-3-carboxylic chloride (I), and 7-*methoxycoumarin*-4-*acethydrazide* (II).

IN a recent paper (*J.*, 1949, S 12) Baker, Collis, and Banks described some acid chlorides derived from 7-hydroxycoumarin (umbelliferone). These were prepared as fluorescent acylating agents for hydroxy- and amino-compounds, the separation and identification of which by chromatographic methods might thereby be facilitated. The most promising of these acyl chlorides was 7-methoxycoumarin-3-carboxylic chloride (I); the related esters and amides exhibit strong blue fluorescence in solution or when adsorbed on alumina, but the preparation of the reagent required the not very readily accessible 2-hydroxy-4-methoxybenzaldehyde. The present paper deals with other fluorescent reagents; no acid chloride superior to (I) has been found, but 7-*methoxycoumarin*-4-*acethydrazide* (II) is an excellent reagent for carbonyl compounds, and is very easily prepared.

Derivatives of Salicylic Acid.—*o*-Anisoyl chloride gives weakly fluorescent esters and amides.

o-Hydroxybenz- and *o*-anis-hydrazide readily yield with a variety of aldehydes and ketones crystalline condensation products which show a rather weak blue fluorescence in ultra-violet light. Acetaldehyde and propaldehyde gave resinous products only. *o*-Hydroxybenzoylazide (Bondi, *Z. physiol. Chem.*, 1907, **52**, 172) is unstable, but reacts with amino-acids to give their acyl derivatives (Bondi, *loc. cit.*), which are also fluorescent. Derivatives of nitrosalicylic acids are not fluorescent.


(I.)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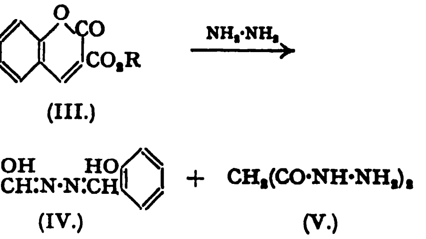
(III.) (IV.) (V.)

Derivatives of Coumarin-3-carboxylic Acid (III; R = H).—This acid, its chloride, esters, and amides are moderately fluorescent in ultra-violet light, but the fluorescence is much less intense than that shown by 7-methoxycoumarin-3-carboxylic acid and derivatives.

Unsuccessful attempts have been made to prepare coumarin-3-carboxyhydrazide. Methyl and ethyl coumarin-3-carboxylates (III; R = Me or Et) fail to react with aqueous-alcoholic hydrazine hydrate at room temperature, but at the boiling point they yield a mixture of *o*-hydroxybenzylideneazine (salazine) (IV) and malonhydrazide (V). This reaction formally involves the breakdown of the α-pyrone ring, under the influence of the strongly basic hydrazine, into the components from which it was formed, namely salicylaldehyde and a derivative of malonic acid. Although coumarin-3-carboxyl chloride readily yielded the amide by treatment with aqueous ammonia, it did not give the hydrazide on treatment with the much stronger base hydrazine hydrate; the only product isolated from the viscous reaction mass was *o*-hydroxybenzylideneazine.

Derivatives of 7-Methoxy-4-methylcoumarin-3-carboxylic Acid.—In attempting to prepare the chloride of this acid by the action of thionyl chloride, Baker, Collis, and Banks (*J.*, 1949, S 12) obtained only 7-methoxy-4-chloromethylcoumarin-3-carboxyl chloride, m. p. 198—200°. Repetition of this experiment has, however, now yielded the expected 7-methoxy-4-methylcoumarin-3-carboxyl chloride, which is rather unstable and melts at 94—95°; it was identified by conversion into the known, related methyl and ethyl esters. The original formation of the chloro-acid chloride was probably due to impurity in the thionyl chloride. Thus it has now been found that 7-methoxy-4-methylcoumarin-3-carboxylic acid is converted into the chloro-acid chloride by reaction with sulphuryl chloride in presence of a trace of benzoyl peroxide as catalyst (see Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142).

Methyl 7-methoxy-4-methylcoumarin-3-carboxylate reacts with hydrazine hydrate to give *7-methoxy-4-methylcoumarin-3-carboxyhydrazide*, and this reagent gives strongly fluorescent derivatives with carbonyl compounds.

Derivatives of 7-Hydroxycoumarin-4-acetic Acid.—This acid was originally prepared by Burton (*Annalen*, 1891, **261**, 167) by condensing resorcinol with acetonedicarboxylic acid in presence of concentrated sulphuric acid, and later the procedure was simplified by Dey and Row (*J. Indian Chem. Soc.*, 1924, **1**, 112) who condensed resorcinol directly with citric acid in presence of sulphuric acid. A careful study of this reaction with particular attention to temperature control has raised the yield of 7-hydroxycoumarin-4-acetic acid to 80%. This acid and all derivatives are intensely fluorescent, even in daylight. *Methyl 7-hydroxycoumarin-4-acetate* proved very stable towards hydrazine hydrate, and the related hydrazide was not obtained.

Methylation of 7-hydroxycoumarin-4-acetic acid with methyl sulphate and alkali gave 7-methoxycoumarin-4-acetic acid. Resinous material only was obtained in attempts to prepare 7-methoxycoumarin-4-acetyl chloride, a result doubtless due to the highly reactive nature of the methylene group. The methyl ester was prepared by direct esterification, and yielded *7-methoxycoumarin-4-acethydrazide* (II) by reaction with hydrazine hydrate. Condensation of (II) with a variety of carbonyl compounds gave the corresponding highly fluorescent *acylhydrazones.*

Experiments with disc chromatograms of alumina have shown the possibility of separating mixtures of the fluorescent esters and hydrazones described.

EXPERIMENTAL.

Derivatives of o-*Hydroxybenzhydrazide.*—This hydrazide was prepared in 73% yield from methyl salicylate (Struve and Radenhausen, *J. pr. Chem.*, 1895, **52**, 239; see also Bondi, *Z. physiol. Chem.*, 1907, **52**, 170) by the use of 60% instead of pure hydrazine hydrate; it separated from ethyl alcohol in plates, m. p. 147°.

The following derivatives were prepared by addition of the carbonyl compound (1 mol.) to *o*-hydroxybenzhydrazide (0·3 g., 1 mol.) in warm alcohol (5 c.c.), collecting them after cooling, and recrystallising them from alcohol: benzylidene derivative, needles, m. p. 248° (Found: N, 11·8. Calc. for $C_{14}H_{12}O_2N_2$: N, 11·7%) (Struve and Radenhausen, *loc. cit.*, m. p. 232°); iso*propylidene* derivative, fine needles, m. p. 228° (Found: C, 62·7; H, 6·2; N, 14·8. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·3; N, 14·6%); *piperonylidene* derivative, needles, m. p. 270° (Found: C, 63·3; H, 4·3; N, 10·1. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·2; N, 9·9%); *acetophenone* o-*hydroxybenzoylhydrazone*, fine, fibrous needles, m. p. 212° (Found: C, 71·1; H, 5·7; N, 10·8. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%). When adsorbed from alcoholic solution on to alumina these derivatives all exhibited a blue fluorescence in ultra-violet light. Acetaldehyde and propaldehyde did not yield solid derivatives under the above conditions.

Hydrazide of 5-Nitrosalicylic Acid.—Nitration of methyl salicylate by the method of Barany and Pianka (*J.*, 1946, 965) gave not only methyl 5-nitrosalicylate, m. p. 99° from ether (40% yield), but also methyl 3-nitrosalicylate, m. p. 132° (25%), from methyl alcohol, separated by taking advantage of its very sparing solubility in ether. Methyl 5-nitrosalicylate (1 g.), in methyl alcohol (20 c.c.), was shaken and then refluxed for ½ hour with 60% hydrazine hydrate (1 c.c.), cooled, and the solid collected and crystallised from methyl alcohol. The *hydrazide* formed yellow needles, m. p. 154° (decomp.) (Found: C, 42·4; H, 4·9; N, 18·4. $C_7H_7O_4N_3,CH_3{\cdot}OH$ requires C, 41·9; H, 4·8; N, 18·3%).

o-*Anishydrazide and Derivatives.*—Methyl *o*-anisate (30 g., 1 mol.) (Sachs and Harold, *Ber.*, 1907, **40**, 2718) and 60% hydrazine hydrate (26 c.c., 1·5 mols.) were refluxed for 2½ hours and then cooled, and the solid was collected after some hours, washed with ether, and crystallised from benzene, giving o-*anishydrazide* (18 g., 60%) as fine needles, m. p. 85° (Found: C, 58·0; H, 5·9; N, 17·2. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0; N, 16·9%). The following derivatives were prepared by warming the reactants in alcoholic solution, completing the separation of solid by addition of water, and crystallising the products from dilute ethyl alcohol: *benzylidene* derivative, prismatic needles, m. p. 176° (Found: C, 71·0; H, 5·4; N, 11·1. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%); iso*propylidene* derivative, needles, m. p. 218° (Found: N, 13·8. $C_{11}H_{14}O_2N_2$ requires N, 13·6%). These compounds, when adsorbed on to alumina, showed a blue fluorescence in ultra-violet light. Crystalline derivatives were not obtained from *o*-anishydrazide and acetaldehyde or propaldehyde.

Derivatives of Coumarin-3-carboxylic Acid.—The acid chloride was prepared by refluxing coumarin-3-carboxylic acid (2 g.; Knoevenagel, *Ber.*, 1898, **31**, 2618) with thionyl chloride (15 c.c.) for 1 hour, cooling it, adding light petroleum (50 c.c.; b. p. 40—60°), collecting the solid, and crystallising it from benzene; it formed needles (1·7 g.), m. p. 147° (Boehm, Schumann, and Hansen, *Arch. Pharm.*, 1933, **271**, 490, record m. p. 147—148°). It was converted into the following derivatives which have been previously prepared in other ways: amide, needles from alcohol, m. p. 274° (decomp.) (Found: C, 63·4; H, 3·7; N, 7·2. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%) (D.R.-P. 172,724 gives m. p. 268—269°; Bechert, *J. pr. Chem.*, 1917, **50**, 27, gives m. p. 236°); methyl ester, m. p. 116° (lit., m. p. 116—117°), which was also prepared by direct esterification of the acid (10 g.) in presence of hydrogen chloride (yield 11 g.); ethyl ester, m. p. 94° (lit., 94°); *n*-propyl ester, m. p. 75° (Found: C, 67·1; H, 5·2. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%) (lit., m. p. 73°); *iso*propyl ester, m. p. 89° (lit., m. p. 89°); anilide, m. p. 248°, prepared in benzene solution (Found: C, 72·2; H, 4·2; N, 5·1. Calc. for $C_{16}H_{11}O_3N$: C, 72·5; H, 4·2; N, 5·3%) (lit., m. p. 250°); benzylamide, m. p. 154° (lit., 154°); piperidide, needles (from water), m. p. 168° (Found: C, 70·1; H, 5·7; N, 5·0. Calc. for $C_{15}H_{15}O_3N$: C, 70·0; H, 5·8; N, 5·45%) (von Werder, *Merck's Jahresbericht*, 1935—6, 98, gives m. p. 168—170°). The p-*toluidide* separates from ethyl acetate in fine, greenish-yellow needles, m. p. 230° (Found: C, 73·0; H, 4·7; N, 5·1. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7; N, 5·0%). The *morpholide* crystallises from water in fine needles, m. p. 92° (Found: C, 64·7; H, 5·0; N, 5·1. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·4; N, 5·4%).

Reaction of Hydrazine with Methyl and Ethyl Coumarin-3-carboxylates.—No reaction occurred between alcoholic solutions of the esters and 60% aqueous hydrazine hydrate in the cold. The ester (2 g.) in alcohol (10 c.c.) was boiled under reflux for ½ hour with 60% hydrazine hydrate (2 c.c.), and after cooling, the mixture of yellow and colourless solids was collected, washed, and the former separated by solution in hot ethyl acetate. This yellow product, *o*-hydroxybenzylideneazine, separated from ethyl acetate in needles, m. p. and mixed m. p. with an authentic specimen (Borsche, *Ber.*, 1921, **54**, 668) 215° (Found: C, 69·8; H, 5·2; N, 11·4. Calc. for $C_{14}H_{12}O_2N_2$: C, 70·0; H, 5·0; N, 11·7%), and gave a dibenzoyl derivative, m. p. 189° (lit., 188—189°). The colourless compound after crystallisation from alcohol had m. p., and mixed m. p. with an authentic specimen of malonhydrazide (Curtius, Schöfer, and Schwan, *J. pr. Chem.*, 1895, **51**, 187), 152°; it further gave a dibenzylidene derivative, m. p. 226° (lit., 226°).

o-Hydroxybenzylideneazine was also obtained as the only readily isolable product by the action of 60% hydrazine hydrate upon coumarin-3-carboxylic chloride in various solvents.

Action of (a) *Thionyl and* (b) *Sulphuryl Chlorides on 7-Methoxy-4-methylcoumarin-3-carboxylic Acid.*—(*a*) The carboxylic acid (1 g.; Baker, Collis, and Banks, *loc. cit.*) was boiled under reflux for 1 hour with thionyl chloride (10 c.c.), excess of light petroleum (b. p. 40—60°) added, and the solid collected. A further precipitation from benzene by the addition of light petroleum gave the acid chloride as pale yellow needles, m. p. 94—95°, which rises on keeping the crystals even in a vacuum (after 24 hours the m. p. was 110—113°; after 48 hours, 180—182°). Owing to this instability the chloride was not analysed, but was identified by conversion into the methyl and ethyl esters, m. p.s and mixed m. p.s with authentic specimens, 128° and 57°, respectively.

(*b*) The acid (0·5 g.) was treated with sulphuryl chloride (5 c.c.) and a trace of benzoyl peroxide. After the vigorous reaction was over the mixture was boiled under reflux for 1 hour, and cooled, and the solid collected after several hours, precipitated from warm toluene by the addition of light petroleum, and dried in a vacuum over sodium hydroxide. This 7-methoxy-4-chloromethylcoumarin-3-carboxyl chloride had m. p. 198°, and was shown to be identical with the material, m. p. 198—200°, previously prepared by Baker, Collis, and Banks; reaction with ethyl alcohol gave ethyl 7-methoxy-4-chloromethylcoumarin-3-carboxylate, m. p. 117° (lit., 117—119°).

7-*Methoxy*-4-*methylcoumarin*-3-*carboxyhydrazide and Derivatives.*—Methyl 7-methoxy-4-methylcoumarin-3-carboxylate (2·5 g.; Baker, Collis, and Banks, *loc. cit.*), dissolved in methyl alcohol (35 c.c.), was treated with 60% aqueous hydrazine hydrate (1·6 c.c., 2 mols.), and the solid which had separated after 3 hours was collected, washed with methyl alcohol and crystallised from methyl or ethyl alcohol. The *hydrazide* (yield 55—60%) formed pale yellow needles, m. p. 210° (Found : C, 58·4; H, 5·0; N, 11·0. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·8; N, 11·3%). The following derivatives were prepared by warming the reactants in alcoholic solution: *benzylidene*, colourless needles (from alcohol), m. p. 250° (Found : C, 67·5; H, 4·8; N, 8·2. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3%); iso*propylidene* (separated after heating for 1 hour and collected after addition of water), prismatic needles, m. p. 237°, from dilute alcohol (Found : N, 9·8. $C_{15}H_{16}O_4N_2$ requires N, 9·7%).

7-*Hydroxycoumarin*-4-*acetic Acid.*—Finely powdered citric acid (100 g.) and concentrated sulphuric acid (135 c.c.) were gently shaken for ½ hour, then slowly heated to 65—70° and maintained at this temperature for ½ hour; the evolution of carbon monoxide had then abated. After the mixture had been cooled to room temperature (½ hour) and then in a freezing mixture to about −5°, resorcinol (45 g., 1 mol.) was added (½ hour) with stirring at such a rate that the temperature remained below 5°, and then concentrated sulphuric (58 c.c.) was similarly added (½ hour), and the mixture placed in the refrigerator and next day poured into ice-water (2 l.). The solid was collected, washed, and dried, giving almost pure 7-hydroxycoumarin-4-acetic acid (83 g., 80%), m. p. 209°. Crystallisation from ethyl alcohol gave the pure acid as needles, m. p. 210°. The *methyl* ester, prepared by the Fischer–Speier method in 90% yield, crystallised from methyl alcohol in fine needles, m. p. 220° (Found : C, 61·1; H, 4·1. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%); attempts to convert it into the related hydrazide were unsuccessful.

7-*Methoxycoumarin*-4-*acetic Acid.*—This acid was prepared by Dey (*J.*, 1915, **107**, 1632) by hydrolysis of its methyl ester (itself prepared in unstated yield from 7-hydroxycoumarin-4-acetic acid, methyl sulphate, and concentrated alkali), or by condensing resorcinol monomethyl ether with acetonedicarboxylic acid. 7-Hydroxycoumarin-4-acetic acid (30 g.) was dissolved in a solution of sodium hydroxide (28 g., 5 mols.) in water (280 c.c.), and methyl sulphate (20 c.c., 1·5 mols.) added dropwise with stirring (½ hour). The mixture was heated on the water-bath for 1½ hours and then cooled, sodium hydrogen sulphite added to remove a red colour, and the whole acidified with dilute sulphuric acid (total volume *ca.* 1 l.). The 7-methoxycoumarin-4-acetic acid was collected after 2 hours, washed, and recrystallised from alcohol, giving thin prisms (18 g., 57%), m. p. 186° (lit., 187°). The methyl ester, prepared in 90% yield by the Fischer–Speier method, had m. p. 122° (lit., 122°). Unsuccessful attempts were made to prepare the acid chloride by the use of thionyl chloride under a variety of conditions, and by the action of phosphorus oxychloride on the sodium salt of the acid, but only coloured resinous products resulted.

7-*Methoxycoumarin*-4-*acethydrazide.*—To the preceding methyl ester (5 g.), dissolved in methyl alcohol (110 c.c.), was added 60% aqueous hydrazine hydrate (5 c.c.; 1·5 mols.), and the solid which separated was collected after 4 hours, washed with dilute methyl alcohol, and crystallised from methyl or ethyl alcohol, giving fibrous needles (2·8 g., 56%), m. p. 206° (Found: C, 58·1; H, 5·0; N, 11·5. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·8; N, 11·3%). After melting, the substance solidified to a yellowish-brown mass which then had m. p. *ca.* 270—275°. The yield of hydrazide was diminished when the reaction mixture was heated.

The following derivatives were prepared by warming the acylhydrazide with the carbonyl compound in alcoholic solution in presence of a trace of acetic acid, and, if necessary, dilution with water, and crystallisation from alcohol except where otherwise stated: *benzylidene*, fine needles, m. p. 264° (Found: C, 68·1; H, 4·8; N, 8·1. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3%); iso*propylidene*, fine needles (from dilute alcohol), m. p. 209° (Found: C, 62·3; H, 5·5; N, 9·6. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%); *ethylidene*, glistening plates, m. p. 194° (Found: C, 61·5; H, 5·2; N, 10·0. $C_{14}H_{14}O_4N_2$ requires C, 61·3; H, 5·1; N, 10·2%); *methylene*, fine prismatic needles, m. p. 156° (Found: C, 59·8; H, 4·8; N, 11·0. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%). 7-*Methoxycoumarin*-4-*acethydrazones* were also prepared from: acetophenone, small prisms, m. p. 215° (Found: C, 68·3; H, 5·1; N, 7·9. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1; N, 8·0%); methyl ethyl ketone, fine needles (from dilute alcohol), m. p. 176° (Found: C, 63·4; H, 5·9; N, 9·4. $C_{16}H_{18}O_4N_2$ requires C, 63·6; H, 6·0; N, 9·3%); pyruvic acid (boiled under reflux for ½ hour), prisms (from dilute alcohol), m. p. 220° (Found: C, 56·3; H, 4·6; N, 8·5. $C_{15}H_{14}O_6N_2$ requires C, 56·6; H, 4·4; N, 8·8%); dihydro-orcinol (1 : 3-diketo-5-methyl*cyclo*hexane) (boiled under reflux for ½ hour), faintly yellow needles (from dilute alcohol), m. p. 258° (decomp.) (Found: C, 64·0; H, 5·9; N, 8·2. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6; N, 7·9%).

Analyses are by Drs. Weiler and Strauss, Oxford, and by Mrs. W. M. Eno, Bristol.

THE UNIVERSITY, BRISTOL.

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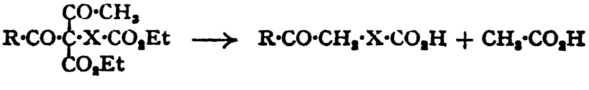
38. *Synthetic Long-chain Aliphatic Compounds. Part I. Introduction. Myristic, Stearic, and Tricosanoic Acids.*

By D. E. Ames, R. E. Bowman, and R. G. Mason.

As a start in the systematic synthesis of long-chain, saturated and unsaturated acids, myristic, stearic, and *n*-tricosanoic acids have been prepared from the corresponding keto-acids by the ketone synthesis devised by Bowman (*J.*, in the press). A convenient method for the preparation of ω-bromoheptoic acid on a large scale has been devised.

Previous methods of synthesis of long-chain fatty acids may conveniently be classified into those using a β-keto-ester as intermediate and those using organo-metallic compounds. The most important of the first group is the well-known Robinson–Robinson synthesis (*J.*, 1925, **127**, 175; 1930, 745) in which an acylacetoacetic ester is submitted to graded hydrolysis to yield the keto-acid :



$$R\cdot CO\cdot\overset{CO\cdot CH_3}{\underset{CO_2Et}{C}}\cdot X\cdot CO_2Et \longrightarrow R\cdot CO\cdot CH_2\cdot X\cdot CO_2H + CH_3\cdot CO_2H$$

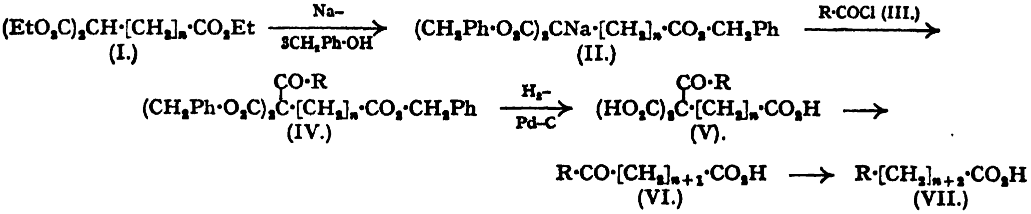
Though this synthesis gives good results in some cases it often suffers from the disadvantage of low yields and occasionally the separation of the products is difficult. This may be caused by hydrolysis in two directions with partial elimination of the " wrong " acyl group.

The second group, *viz.*, methods involving organo-metallic reagents, has been much used in recent years :

$$R_2M + Cl\cdot CO\cdot[CH_2]_x\cdot CO_2Et \longrightarrow R\cdot CO\cdot[CH_2]_x\cdot CO_2Et$$

The most important of these reagents are the cadmium dialkyls (Cason, *Chem. Reviews*, 1947, **40**, 15) although the zinc alkyls have been shown to give excellent yields of keto-acids containing up to thirty-five carbon atoms (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2350). The dialkylcadmium synthesis is probably the most convenient method for the preparation of straight-chain keto-acids up to C_{25} when the "chain-extender," *i.e.*, the acid chloride ester, is readily available and R is not too large. The disadvantages of this method are the difficulty of preparing the " chain-extender " (cf. Drake and Melamed, *J. Amer. Chem. Soc.*, 1948, **70**, 364) and the well-known tendency of the Wurtz reaction to become appreciable when Grignard reagents are prepared from the higher alkyl halides, with, often, difficulty in separating the resultant saturated paraffin R–R from the product (*inter al.*, Houston, *J. Amer. Chem. Soc.*, 1947, **69**, 517).

The new ketone synthesis described recently (*J.*, in the press) appears to be particularly well suited for the synthesis of long-chain aliphatic compounds. As applied to saturated fatty acids, it may be represented as follows :



$$\underset{(I.)}{(EtO_2C)_2CH\cdot[CH_2]_n\cdot CO_2Et} \xrightarrow[3CH_2Ph\cdot OH]{Na-} \underset{(II.)}{(CH_2Ph\cdot O_2C)_2CNa\cdot[CH_2]_n\cdot CO_2\cdot CH_2Ph} \xrightarrow{R\cdot COCl\ (III.)}$$

$$\underset{(IV.)}{(CH_2Ph\cdot O_2C)_2\overset{CO\cdot R}{C}\cdot[CH_2]_n\cdot CO_2\cdot CH_2Ph} \xrightarrow[Pd-C]{H_2-} \underset{(V).}{(HO_2C)_2\overset{CO\cdot R}{C}\cdot[CH_2]_n\cdot CO_2H} \longrightarrow$$

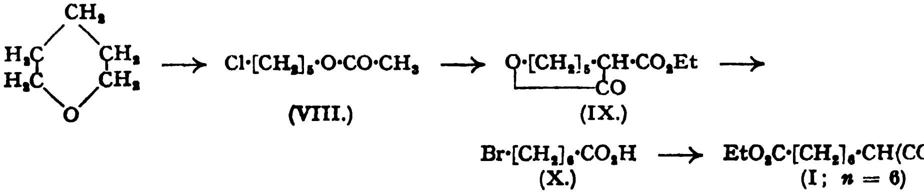
$$\underset{(VI.)}{R\cdot CO\cdot[CH_2]_{n+1}\cdot CO_2H} \longrightarrow \underset{(VII.)}{R\cdot[CH_2]_{n+2}\cdot CO_2H}$$

The advantages of the debenzylation synthesis are several. First, the yields are usually 70% or higher; secondly, the " chain-extender " is a malonic ester which may be obtained in several ways and may be purified through the crystalline triacid (cf. the β-keto-ester synthesis); thirdly, the intermediate reactant (IV) is rendered soluble by the three benzyl groups, so that subsequent reactions can be carried out in not too dilute solution.

One of the aims, therefore, of the present series of papers is to utilise this reaction for the preparation of fatty compounds of greater chain lengths than has hitherto been possible. Parallel researches are in hand on the synthesis of the higher unsaturated acids using the procedure already described in a preliminary note (Bowman, *Nature*, 1949, **163**, 95).

Before proceeding with the main objective we have examined two further applications of this synthesis and obtained thereby myristic and stearic acids.

For the synthesis of the former we chose the route employing hexanoyl chloride (III; R = C_5H_{11}) and ethyl heptane-1 : 1 : 7-tricarboxylate (I; *n* = 6). The latter has been previously obtained, in poor yield, by thermal degradation of the corresponding oxalo-ester obtained from ethyl azelaate (Zakutskaya and Gudovich, *J. Gen. Chem., Russia*, 1938, **8**, 216). Since it was required in considerable quantity for another investigation, we have examined a number of routes for its preparation and have developed a method based on tetrahydropyran which makes ω-bromoheptanoic acid readily accessible.


H_2C
CH_2
H_2C
CH_2
CH_2
O
$Cl{\cdot}[CH_2]_5{\cdot}O{\cdot}CO{\cdot}CH_3$
(VIII.)
$O{\cdot}[CH_2]_3{\cdot}CH{\cdot}CO_2Et$
CO
(IX.)
$Br{\cdot}[CH_2]_6{\cdot}CO_2H$
(X.)
$EtO_2C{\cdot}[CH_2]_6{\cdot}CH(CO_2Et)_2$
(I; $n = 6$)

Tetrahydropyran was converted into 5-chloroamyl acetate (VIII) by acetyl chloride in the presence of zinc chloride (Synerholm, *J. Amer. Chem. Soc.*, 1947, **69**, 2581), and the chloro-ester treated with sodiomalonic ester in alcohol to give the lactone ester (IX). Hydrobromic–acetic acids, followed by hydrobromic–sulphuric acids (Brown and Partridge, *J. Amer. Chem. Soc.*, 1944, **66**, 839), then furnished 7-bromoheptanoic acid * (X) in 60% overall yield. Finally the bromo-acid was azeotropically esterified in almost quantitative yield and treated with sodiomalonic ester in the usual manner to give the required triester (I; $n = 6$). Conversion of this into the corresponding tribenzyl sodio-ester and reaction of this material with *n*-hexanoyl chloride afforded a keto-ester (IV; $R = C_5H_{11}$; $n = 6$) which was debenzylated and decarboxylated to give *9-ketotetradecanoic acid* * (VI; $R = C_5H_{11}$; $n = 6$). Wolff–Kishner reduction at atmospheric pressure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) then furnished myristic acid.

An alternative keto-acid synthesis would utilise the reaction of an acid chloride ester with a benzyl alkylsodiomalonate, thus:

$$\underset{\text{(XI.)}}{EtO_2C{\cdot}[CH_2]_n{\cdot}COCl} + \underset{\text{(XII.)}}{Na{\cdot}CR(CO_2{\cdot}CH_2Ph)_2} \longrightarrow \underset{\text{(XIII.)}}{(CH_2Ph{\cdot}O_2C)_2CR{\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2Et}$$

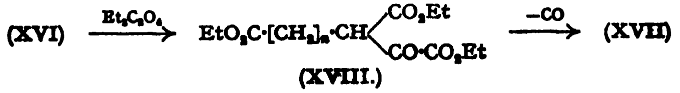
$$\xrightarrow[\text{Pd-C}]{H_2-} \underset{\text{(XIV.)}}{R{\cdot}CH_2{\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2H} \longrightarrow \underset{\text{(XV.)}}{R{\cdot}[CH_2]_{n+2}{\cdot}CO_2H}$$

Accordingly, to test this route, sebacic ester chloride (XI; $n = 8$) was condensed with benzyl *n*-heptylsodiomalonate (XII; $R = C_7H_{15}$) and the resulting keto-triester (XIII; $R = C_7H_{15}$, $n = 8$) submitted to the usual reactions to give the known 10-keto-octadecanoic acid (XIV; $R = C_7H_{15}$, $n = 8$), which was then reduced to stearic acid.

Our main objective being to ascend the fatty acids series as rapidly as possible, it will be necessary to prepare "chain-extenders" of the general formula (I) where *n* is as great as possible. Aliphatic αω-dicarboxylic esters are available by a number of routes and accordingly we have examined methods for their conversion into the corresponding malonic esters (I). The carbethoxylation technique of Wallingford *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 2056) using ethyl carbonate appeared to be of interest since it is a one-stage process and has already been applied to sebacic ester (XVI; $n = 7$) by the same authors, to give a product formulated by them as

$$\underset{\text{(XVI.)}}{EtO_2C{\cdot}[CH_2]_n{\cdot}CH_2{\cdot}CO_2Et} \xrightarrow[\text{NaOEt}]{Et_2CO_3-} \underset{\text{(XVII.)}}{EtO_2C{\cdot}[CH_2]_n{\cdot}CH(CO_2Et)_2}$$

(XVII; $n = 7$). In our hands, however, this product, although similar, was impure as shown by a low saponification value and a wide boiling range; and the derived tricarboxylic acid had neither the required equivalent weight nor a sharp melting point. We therefore abandoned this method and investigated an alternative route by way of the oxalo-ester (XVIII).



$$\text{(XVI)} \xrightarrow{Et_2C_2O_4} EtO_2C{\cdot}[CH_2]_n{\cdot}CH\begin{cases}CO_2Et\\ CO{\cdot}CO_2Et\end{cases} \xrightarrow{-CO} \text{(XVII)}$$

(XVIII.)

After some preliminary experiments we obtained the required ethyl *n*-octane-1 : 1 : 8-tricarboxylate (XVII; $n = 7$) in good yield and in a high state of purity from ethyl sebacate, without purification of the intermediate oxalo-ester (XVIII; *n* = 7) (cf. Zakutskaya, *J. Gen. Chem., Russia*, 1940, **10**, 1553). Myristoyl chloride was condensed with benzyl sodio-octane-1 : 1 : 8-tricarboxylate (II; *n* = 7), and the resulting keto-triester (IV; R = $C_{13}H_{27}$; *n* = 7) was debenzylated and decarboxylated by the general method. 10-*Ketotricosanoic acid* (VI; R = $C_{13}H_{27}$; *n* = 7) was thus obtained in exceptionally high yield (crude, 93%; pure, 85%) Reduction to the known *n*-tricosanoic acid, in quantitative yield, was carried out as above.

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* Geneva numbering is used in this series of papers.—Ed.

EXPERIMENTAL.

The Vigreux column used in this work was of the usual type, 22 cm. in length. The Fenske column, the techniques used for conversion of malonic esters into the benzyl sodio-esters, the reactions of the latter with the acid chlorides, and debenzylations and decarboxylations were as described previously (Bowman, *loc. cit.*).

5-*Chloroamyl Acetate* (VIII).—This material was prepared from tetrahydropyran as described by Synerholm (*loc. cit.*) except that the quantity of anhydrous zinc chloride was reduced (5 g. per 2·5 mols. of acetyl chloride) and the product was distilled directly from the reaction mixture through the Vigreux column.

7-*Bromoheptanoic Acid* (X).—The foregoing chloro-compound (434 g., 2·63 mols.) was treated with sodiomalonic ester (3·2 mols.) in absolute ethanol (500 ml.) in the presence of sodium iodide (20 g.) at 110° for 6 hours. After removal of most of the ethanol and ethyl acetate by distillation, the cooled reaction mixture was added to dilute sulphuric acid, and the product, after saturation of the aqueous layer with ammonium sulphate, isolated with benzene (2 × 400 ml.). The solvent-free oil thus obtained was mixed with glacial acetic acid (500 ml.) and constant-boiling hydrobromic acid (500 ml.), and the resulting mixture slowly distilled through a Vigreux column, ethyl acetate (400 ml.) containing some ethyl bromide being collected during 4 hours; during this last phase decarboxylation had already started and was completed by further refluxing for 1 hour after the addition of sulphuric acid (50 ml.; 20N.). The cooled solution was then mixed with a further portion of constant-boiling hydrobromic acid (500 ml.) and concentrated sulphuric acid (150 ml.), and the mass heated at 110° (internal temperature) for 4 hours. After cooling to room temperature, the reaction mass was diluted with water, and the lower layer of bromo-acid separated; further product was obtained by extraction of the aqueous layer, previously saturated with ammonium sulphate, with ether (3 × 400 ml.). The combined organic extracts were then washed with water, dried (Na_2SO_4), and treated with active charcoal to remove most of the colour, and the solvent removed by distillation. The residue was found to contain some water and, accordingly, was mixed with benzene (1 l.), and the mixture refluxed with a phase-separator (Dean and Stark) until dry. After removal of solvent and a small fore-run, 7-bromoheptanoic acid was obtained as an almost colourless oil, b. p. 140—142°/1·5 mm. (378 g.; 60%, calc. on the tetrahydropyran), which solidified and had m. p. 28—29° (thermometer in liquid). The bromo-acid was characterised by conversion in the usual manner into the corresponding phenoxy-acid which separated from light petroleum (b. p. 40—60°) in needles, m. p. 56° (von Braun, *Ber.*, 1906, **39**, 4362, gave m. p. 56—57°).

Ethyl 7-*Bromoheptanoate*.—A mixture of the bromo-acid (376 g.), benzene (700 ml.), ethanol (300 ml.) and AnalaR concentrated sulphuric acid (3 ml.) was distilled through the Fenske column fitted with a phase-separator until no further phase-separation took place. The cooled solution was washed with water, sodium hydrogen carbonate solution, and again water, dried (Na_2SO_4), and distilled to give, after rejection of a fore-run (10 g.), the ethyl ester as a colourless liquid, b. p. 112°/5 mm., n_D^{20} 1·4608 (397 g., 93%).

Ethyl n-*Heptane*-1 : 1 : 7-*tricarboxylate* (I; n = 6).—The foregoing ester (237 g.; 1 mol.) was treated with sodiomalonic ester (1·75 mols.) in dry ethanol (700 ml.) in the presence of sodium iodide (10 g.) at 90—105° for 10 hours. After removal of solvent by distillation, the cooled mixture was treated with excess of dilute sulphuric acid and isolated in the usual manner to give the triester as a colourless oil, b. p. 146—147°/0·5 mm., n_D^{20} 1·4411 (263 g., 83%).

9-*Ketotetradecanoic Acid* (VI; R = C_5H_{11}; *n* = 6).—Ethyl *n*-heptane-1 : 1 : 7-tricarboxylate (31·6 g., 0·1 mol.) was converted into the corresponding tribenzyl sodio-ester by means of sodium (2·3 g., 0·1 mol.), benzyl alcohol (32·5 g., 0·3 mol.) in benzene (300 ml.), and the product treated with hexanoyl chloride (b. p. 94°/120 mm.; 13·5 g., 0·1 mol.) according to the general procedure. The product was hydrogenated in ethanol (160 ml.) containing ethyl acetate (20 ml.), palladised charcoal (5 g.; 10%), and palladised strontium carbonate (5 g. of 10%). The catalyst was removed by filtration, the filtrate refluxed for 0·5 hour to bring about decarboxylation, and the solvent removed at atmospheric pressure and finally *in vacuo*. The residue was boiled with acetic acid (75 ml.) containing sulphuric acid (2·5 ml. of 20N.) for 0·5 hour to bring about ketone hydrolysis of any residual β-keto-ester, and the product was isolated by dilution with water and filtration; yield, 17 g. (70%); m. p. 59—61°. On crystallisation from light petroleum (b. p. 40—60°) 9-*ketotetradecanoic acid* separated in rosettes of needles, m. p. 66° (Found: C, 69·4; H, 10·7. $C_{14}H_{26}O_3$ requires C, 69·4; H, 10·7%). The p-*bromophenacyl* ester crystallised from 96% ethanol (norite) in needles, m. p. 78° (Found: C, 60·7; H, 6·9. $C_{22}H_{31}O_4Br$ requires C, 60·1; H, 7·3%).

A sample of the keto-acid was reduced with hydrazine and sodium hydroxide in 2 : 2′-dihydroxydiethyl ether, following exactly the procedure of Huang-Minlon (*loc. cit.*), to give myristic acid (80%) which separated from light petroleum (b. p. 40—60°) at −20° in plates, m. p. 53·5—54° (capillary) undepressed by admixture with authentic material.

10-*Keto-octadecanoic Acid* (XIV; R = C_7H_{15}; *n* = 8).—*n*-Heptylmalonic ester (b. p. 118—119°/1·5 mm.; 18·1 g., 0·07 mol.) was converted by sodium (1·61 g., 0·07 mol.) in benzene (300 ml.) into the sodium salt of its enolic form and treated with benzyl alcohol (15·5 g., 0·14 mol.) in the usual manner, to give benzyl sodio-*n*-heptylmalonate. This was then treated with sebacic ethyl ester chloride (17·4 g., 0·07 mol.), and the product debenzylated and decarboxylated as usual to give the crude product which was hydrolysed and isolated as in the previous experiment. The mixed acids, so obtained, were converted into their ethyl esters by azeotropic esterification and unchanged materials removed by distillation up to 190° (bath)/1 mm. The residual crude ethyl ester was hydrolysed with alkali and the keto-acid obtained in the usual manner, collected, and dried; yield, 14·9 g. (71%); m. p. 79—82°. 10-Keto-octadecanoic acid crystallised from light petroleum (b. p. 80—100°) in plates, m. p. 83°, and was characterised by conversion into the oily oxime and thence into the derived amide, plates (from methanol), m. p. 80° (cf. Robinson and Robinson, *J.*, 1926, 2207).

Ethyl n-*Octane*-1 : 1 : 8-*tricarboxylate* (XVII; $n = 7$).—Ethyl oxalate (73 g., 0·5 mol.) was added to a stirred suspension of ethanol-free sodium ethoxide (from 11·5 g. of sodium; 0·5 mol.) in dry benzene (400 ml.), followed by ethyl sebacate (XVI) (161 g., 0·62 mol.). The resulting homogeneous solution was kept at room temperature for 24 hours and extracted with ice-water (1 l.). The organic layer was then extracted with aqueous sodium hydroxide (1 l.; 0·5N.) at 0°, and the combined aqueous extracts were washed with fresh benzene (200 ml.). Acidification of the combined aqueous extracts was effected in the presence of benzene (200 ml.) and ice with hydrochloric acid (250 ml.; 5N.). After the washing with water, the benzene solution was evaporated to dryness *in vacuo*, to give the crude oxalo-ester (XVIII; $n = 7$) (126 g.). The combined benzene extracts of neutral materials furnished, on distillation and fractionation, recovered ethyl sebacate (66 g.).

The crude oxalo-ester was heated at 160—180°/5 mm. in the presence of powdered glass for 3 hours, whereafter no further gas evolution took place. Distillation of the residue through a fractionating column (15 × 1·2 cm. containing 3-mm. Fenske helices) furnished ethyl *n*-octane-1 : 1 : 8-tricarboxylate as a colourless oil, b. p. 160°/1 mm., n_D^{20} 1·4436, d_4^{20} 1·015 (Found : C, 61·5; H, 9·0; sap. val., 110. Calc. for $C_{17}H_{30}O_6$: C, 61·8; H, 9·1%; sap. equiv., 110). The yield of this material was 88 g. (72% based on unrecovered ethyl sebacate). Lower- (sap. equiv., 120) and higher-boiling fractions (sap. val., 105) were rejected.

A sample of the triester was hydrolysed with aqueous-alcoholic sodium hydroxide, and the n-*octane*-1 : 1 : 8-*tricarboxylic acid*, obtained by addition of *excess* of sulphuric acid, crystallised from ethylene dichloride–ethyl acetate whence it separated in rosettes of colourless needles, m. p. 108—109° (Found : C, 53·0; H, 6·9; equiv., 82. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3%; equiv., 82). On heating at 160—180° it was converted into sebacic acid, leaflets (from water), m. p. and mixed m. p. 133°.

10-*Ketotricosanoic Acid* (VI; $R = C_{13}H_{27}$; $n = 7$).—Benzyl sodio-*n*-octane-1 : 1 : 8-tricarboxylate (0·1 mol.) was prepared in the usual manner from the foregoing triester (33·0 g., 0·1 mol.), sodium (2·3 g., 0·1 mol.), and benzyl alcohol (33·4 g., 0·3 mol.) in benzene solution and treated with myristoyl chloride [24·65 g., 0·1 mol.; b. p. 134°/2·5 mm. from acid, m. p. 53·6° (thermometer in liquid)]. The next stages, *i.e.*, hydrogenation, decarboxylation, and working up were carried out as for 9-ketotetradecanoic acid. The yield of crude material, m. p. 86°, was 36·2 g. (93%). The product contained some ester and was hydrolysed. Thus, 10·0 g. of crude acid were boiled with sodium hydroxide (100 ml.; N.) for 1 hour and acidified at the b. p., with shaking. 10-*Ketotricosanoic acid* was crystallised once from benzene (30 ml.) and then twice from acetone (100 ml. each time), from which it (8·7 g.) separated in colourless plates, m. p. 93·5° (constant) (Found : C, 74·7; H, 11·9. $C_{23}H_{44}O_3$ requires C, 75·0; H, 11·9%). The solubility of the keto-acid in acetone at 15° is *ca.* 0·2 g. per 100 ml.

It formed an *oxime* which crystallised from light petroleum (b. p. 40—60°) at 0° in plates, m. p. 43° (Found : N, 3·55. $C_{23}H_{45}O_3N$ requires N, 3·65%).

n-*Tricosanoic Acid.*—The foregoing keto-acid (20·2 g.) was reduced in the same manner as before using 2 : 2′-dihydroxydiethyl ether (150 ml.), hydrazine hydrate (14 ml.; 50%), and potassium hydroxide (12 g.) under reflux for 1·5 hours and then at 195° for 6 hours. The acid (19·4 g.; 100%) had m. p. 79° and was practically pure. It was crystallised from benzene (50 ml.) to give material, m. p. 79·1°, and then twice from acetone (70 ml., each time) from which it separated in colourless plates (17·9 g., m. p. 79·2° (constant). The solubility of *n*-tricosanoic acid in benzene at 15° is *ca.* 0·5 g. per 100 ml. and in acetone at 15° *ca.* 1 g. per 100 ml.

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BIRKBECK COLLEGE, LONDON, E.C.4.

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39. *Synthetic Long-chain Aliphatic Compounds. Part II. Erucic and Brassidic Acids. A New Olefin Synthesis.*

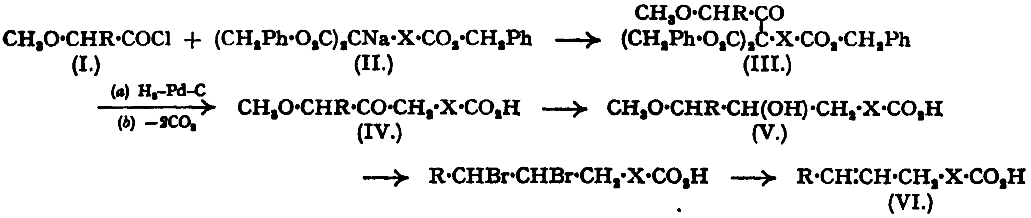
By R. E. BOWMAN.

A new olefin synthesis, whereby methoxy-ketones (IV) are converted into the corresponding methoxy-alcohols (V) and thence, by successive treatment with hydrogen bromide and zinc, into the olefin (VI), has led to the total synthesis of erucic and brassidic acids (for a preliminary account of this work, see *Nature*, 1949, **163**, 95).

CONCURRENTLY with the synthesis of saturated acids (Part I, preceding paper), we were interested in developing a new and general method of synthesis of the corresponding unsaturated compounds, particularly since, at the time when these experiments were begun, the only general syntheses of olefinic acids (Noller and Bannerot, *J. Amer. Chem. Soc.*, 1934, **56**, 1563) were based on the method of Boord (*ibid.*, 1930, **52**, 3396). This synthesis, however, suffers from the disadvantage that the starting materials, αω-chloro-aldehydes, are difficult of access, although a later modification due to Baudart (*Compt. rend.*, 1943, **217**, 399; 1945, **220**, 404) has, to some extent, eased this situation.

Ruzicka, Plattner, and Widmer (*Helv. Chim. Acta*, 1942, **25**, 604, 1086) have recently developed a new method employing a symmetrical acyloin as intermediate. This method has since been modified by Baudart (*Bull. Soc. chim.*, 1946, [v], **13**, 87) to allow of the synthesis of the asymmetrical monobasic unsaturated acids. When this work was nearing completion, Ahmud and Strong (*J. Amer. Chem. Soc.*, 1948, **70**, 1699) reported a new general method based on the semi-hydrogenation of the corresponding acetylenic acid (cf. Bhattacharya, Saletore, and Simonsen, *J.*, 1928, 2678).

Two routes, both employing our new ketone synthesis (*J.*, in the press), were available, one using the acyloin $R\cdot CH(OH)\cdot CO\cdot[CH_2]_n\cdot CO_2H$ and starting from the appropriate α-acetyl-acid chloride, the other using the α-alkoxy-acid chloride (I) and the α-alkoxy-ketone (IV) in the following general manner:



$$\underset{\text{(I.)}}{CH_3O\cdot CHR\cdot COCl} + \underset{\text{(II.)}}{(CH_2Ph\cdot O_2C)_2CNa\cdot X\cdot CO_2\cdot CH_2Ph} \longrightarrow \underset{\text{(III.)}}{(CH_2Ph\cdot O_2C)_2\overset{CH_3O\cdot CHR\cdot CO}{C}\cdot X\cdot CO_2\cdot CH_2Ph}$$

$$\xrightarrow[(b)\ -2CO_2]{(a)\ H_2\text{–}Pd\text{–}C} \underset{\text{(IV.)}}{CH_3O\cdot CHR\cdot CO\cdot CH_2\cdot X\cdot CO_2H} \longrightarrow \underset{\text{(V.)}}{CH_3O\cdot CHR\cdot CH(OH)\cdot CH_2\cdot X\cdot CO_2H}$$

$$\longrightarrow R\cdot CHBr\cdot CHBr\cdot CH_2\cdot X\cdot CO_2H \longrightarrow \underset{\text{(VI.)}}{R\cdot CH{:}CH\cdot CH_2\cdot X\cdot CO_2H}$$

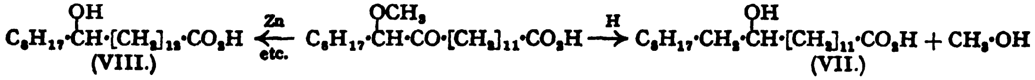
The experiments now described herein had as their objective the realisation of the second route as applied to the synthesis of erucic and brassidic acids (VI; $R = C_8H_{17}$, $X = [CH_2]_{10}$).

The early experiments were concerned with the preparation of 2-methoxydecanoic acid * from the corresponding methyl bromo-ester by treatment with methanolic sodium methoxide.

$$CH_3R\cdot CO_2H \longrightarrow Br\cdot CHR\cdot CO_2CH_3 \longrightarrow CH_3O\cdot CHR\cdot CO_2CH_3 \longrightarrow CH_3O\cdot CHR\cdot CO_2H$$

Considerable difficulty was encountered in obtaining the α-methoxy-acid free from a small amount of impurity, but eventually by careful fractionation of the crude methyl 2-methoxydecanoate through a Fenske column, the pure *ester* was obtained and thence, by hydrolysis, pure *2-methoxydecanoic acid*. The acid was converted into the corresponding chloride (I; $R = C_8H_{17}$) with thionyl chloride without rearrangement (as shown by its hydrolysis by dilute alkali to give the original acid in a pure state). Condensation with tribenzyl sodioundecane-1 : 1 : 11-tricarboxylate (II; $X = [CH_2]_{10}$) furnished the keto-ester which, on hydrogenolysis and decarboxylation according to the general method, yielded 13-*keto*-14-*methoxydocosanoic acid* (IV; $R = C_8H_{17}$, $X = [CH_2]_{10}$) as a low-melting solid.

Before proceeding with the olefin synthesis, the action of a number of reducing agents on this methoxy-ketone was examined. Sodium and ethanol furnished an oil and a small amount of a crystalline solid, m. p. 87—87·5°, which is formulated as 13-*hydroxydocosanoic acid* (VII)



$$\underset{\text{(VIII.)}}{C_8H_{17}\cdot\overset{OH}{C}H\cdot[CH_2]_{12}\cdot CO_2H} \xleftarrow[\text{etc.}]{Zn} C_8H_{17}\cdot\overset{OCH_3}{C}H\cdot CO\cdot[CH_2]_{11}\cdot CO_2H \xrightarrow{H} \underset{\text{(VII.)}}{C_8H_{17}\cdot CH_2\cdot\overset{OH}{C}H\cdot[CH_2]_{11}\cdot CO_2H} + CH_3\cdot OH$$

[cf. the reduction of ethoxyacetone by sodium amalgam and acid to give acetone and ethanol (Fittig and Erlenbach, *Annalen*, 1892, **269**, 22), and a similar reduction of an acyloin by sodium and ethanol to give some of the corresponding monohydroxy-compound (Ruzicka *et al.*, *loc. cit.*)]. Reductions with zinc and acid under a variety of conditions gave rise, in high yield, to an isomeric hydroxy-acid, m. p. 90°, depressed to 78—82° by admixture with the previous product, and formulated as 14-*hydroxydocosanoic acid* (VIII.). A sample of this material was oxidised to the corresponding keto-acid, m. p. 85° (lit., 85°) which raised the m. p. of a sample of 14-keto-docosanoic acid, m. p. 83°, obtained previously by the hydration of behenolic acid with sulphuric acid (Holt and Baruch, *Ber.*, 1893, **26**, 838), a reaction unlikely to result in unidirectional addition (Robinson and Robinson, *J.*, 1925, **127**, 175; 1930, 745).

Attempts to reduce the methoxy-ketone catalytically with Adams's catalyst were not successful. Reduction with aluminium *iso*propoxide, however, furnished a solid product which was separated by light petroleum into a solid 13-*hydroxy*-14-*methoxydocosanoic acid* (V; $R = C_8H_{17}$, $X = [CH_2]_{10}$) and a liquid product containing some unchanged methoxy-acid. The liquid fraction, on treatment with hydrogen bromide followed by zinc dust in alcohol, gave a solid from which brassidic and erucic acids were isolated. Both acids were obtained pure and shown to be identical with materials obtained from natural sources, by mixed melting points of the parent acids, their *p*-bromophenacyl esters, and the derived dihydroxy-acids obtained by the action of peracetic acid (Dorée and Pepper, *J.*, 1942, 477).

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* Geneva nomenclature is used in this paper.—Ed.

Conversion of the solid hydroxy-methoxy-acid into the dibromide proved more difficult. We were, at that time, unaware of Baudart's technique (*loc. cit.*) which has since been used with success, but finally by treatment with gaseous hydrogen bromide at 150—160° for 6 hours followed by zinc dust, a moderate yield of brassidic acid was obtained.

It is realised that the method for conversion of the hydroxy-methoxy-acids into the olefinic acid used in this work is far from satisfactory. Experiments are in hand on the development of a technique suitable for general application and will be reported later.

EXPERIMENTAL.

The equipment and techniques employed were as described in Part I.

Decanoic Acid.—A sample of commercial ethyl decanoate (Messrs. A. Boake, Roberts & Co., Ltd.) was fractionated through the Fenske column (total-reflux head) and the fraction, b. p. 118°/10 mm., collected. The acid obtained by hydrolysis was distilled (Vigreux column) and the fraction, b. p. 118—119°/1·5 mm., m. p. 31° (thermometer in liquid), was used.

Methyl 2-Bromodecanoate.—Decanoic acid (110 g.) was converted into its chloride with thionyl chloride (75 ml.). After removal of excess of the latter *in vacuo*, the mass was heated to 110° and treated with bromine (40 ml.) in the usual manner and finally poured into methanol (300 ml.) and left overnight. Isolated as usual the ester was distilled through a column (Vigreux), and the fraction (140 g.), b. p. 89°/0·5 mm., collected.

2-*Methoxydecanoic Acid.*—The foregoing ester was added with stirring to a solution of sodium methoxide (from 17 g. of metal) in methanol (300 ml.; magnesium-dried), and the mixture boiled under reflux for 4 hours, whereafter most of the solvent was removed by distillation. The cooled residue was diluted with water, and the product isolated with light petroleum (b. p. 40—60°). The oil thus obtained was treated with a mixture of silver oxide (10 g.) and methyl iodide (15 ml.) in acetone solution (100 ml.) under reflux for 6 hours. After removal of solid material by filtration, the product was carefully distilled through the Fenske column to give fractions, (i) b. p. 86—97°/12 mm. (15 ml.) and (ii) pure *methyl* 2-*methoxydecanoate*, b. p. 97°/2 mm., n_D^{20} 1·4312 (70 g.) (Found: C, 66·7; H, 10·9. $C_{12}H_{24}O_3$ requires C, 66·7; H, 11·1%).

The ester (70 g.) was hydrolysed by treatment with sodium hydroxide (50 ml. of 10N.) in methanol (70 ml.) for ½ hour, dilution with water (300 ml.), and boiling with escape of methanol (1 hour). Acidification of the cooled solution with sulphuric acid (50 ml. of 20N.) furnished the acid which was isolated with light petroleum (b. p. 40—60°). 2-*Methoxydecanoic acid* was obtained as a colourless oil, b. p. 118°/0·5 mm., which solidified immediately and then had m. p. 42·5° (thermometer in liquid). A sample crystallised from light petroleum (b. p. 40—60°) at −10° in colourless slender needles, m. p. 43—43·5° (capillary) (Found: C, 65·5; H, 10·7. $C_{11}H_{22}O_3$ requires C, 65·34; H, 10·9%). It was characterised as the *tribromoanilide*: the acid chloride (see below; 1·7 g.) was added to a solution of tribromoaniline (2 g.) and pure dimethylaniline (2 g.) in dry, purified dioxan (10 ml.), and the mixture refluxed for 0·5 hour; the cooled solution was poured into excess of dilute hydrochloric acid, and the solid removed by filtration; after being washed with water and triturated with alkali and then with water, the product crystallised from aqueous alcohol (norite) in rosettes of slender needles, m. p. 81—82° (Found: C, 39·8; H, 4·7. $C_{17}H_{24}O_2NBr_3$ requires C, 39·7; H, 4·8%).

2-*Methoxydecanoyl Chloride* (I; R = C_8H_{17}).—A mixture of the foregoing acid (61 g.) and purified thionyl chloride (50 ml.) was kept successively at room temperature for 1 hour, at 30° for 2 hours, and finally at 60° for the same period. Distillation gave the *acid chloride* as a colourless liquid with a characteristic odour and b. p. 83—84°/0·4 mm. (62 g., 93%). It was characterised as the tribromoanilide (as above) and by mild hydrolysis at room temperature with aqueous sodium hydrogen carbonate whence acidification at 0° gave the original acid, m. p. 42° (air-dried) undepressed by admixture with the original material.

Ethyl ω-Bromoundecanoate.—The bromo-acid (Ashton and Smith, *J.*, 1934, 438; m. p. 51°) was esterified azeotropically in the manner described for the corresponding bromoheptoic acid in Part I (*loc. cit.*). The ester was thus obtained as a colourless oil (98%), b. p. 118—119°/0·15 mm.

Ethyl n-*Undecane*-1 : 1 : 11-*tricarboxylate.*—The above bromo-ester (154 g., 0·53 mol.) was treated with sodiomalonic ester (0·75 mol.) in absolute ethanol (300 ml.) under reflux for 6 hours. Isolated in the usual manner, the triester was carefully distilled and, after rejection of a fore-run (b. p. 80—180°), was collected at 180—182°/0·15 mm., m. p. 0—1° (150 g., 76%).

13-*Keto*-14-*methoxydocosanoic Acid* (IV; R = C_8H_{17}, X = $[CH_2]_{10}$).—The foregoing triethyl ester (93 g., 0·25 mol.) was converted into the sodium salt of its enol in benzene (300 ml.) with powdered sodium (5·75 g., 0·25 mol.) and treated with benzyl alcohol (81 g., 0·75 mol.) according to the general procedure to give the corresponding tribenzyl sodio-ester (II; X = $[CH_2]_{10}$). The latter was treated with 2-methoxydecanoyl chloride (55 g., 0·25 mol.), and the product in ethanol (200 ml.) containing ethyl acetate (100 ml.) was debenzylated and decarboxylated as usual. The residue obtained after removal of solvent was treated with light petroleum (b. p. 40—60°; 500 ml.) at 0° and filtered from solid material. Solvent and unchanged 2-methoxydecanoic acid were removed by distillation up to 200° (bath temperature) at 0·2 mm. pressure to give the crude *keto-methoxy-acid* (68 g., 71%) which solidified at room temperature and was used directly for future experiments. A sample was crystallised from light petroleum (b. p. 40—60°) at −25° and furnished the pure acid in colourless plates, m. p. 32—33° (Found: C, 71·2; H, 11·2. $C_{23}H_{44}O_4$ requires C, 71·9; H, 11·4%).

Reduction Experiments.—Sodium and ethanol. The crude keto-methoxy-acid (2 g.) was dissolved in boiling ethanol (25 ml.) and treated with sodium (2 g.) in portions. Dilution with water and acidification afforded a gummy product which was dissolved in boiling methanol (15 ml.). On cooling, 13-*hydroxydocosanoic acid* (0·4 g.), m. p. 86—87°, separated. It crystallised from ethyl acetate in tiny colourless prisms, m. p. 87—87·5° (Found: C, 74·3; H, 11·9. $C_{22}H_{44}O_3$ requires C, 74·2; H, 12·3%).

Zinc. The keto-methoxy-acid (2 g.) was submitted to the following procedures. (*a*) Clemmensen reduction with amalgamated zinc (15 g.) in hydrochloric acid (5N.) for 6 hours. (*b*) Refluxing with zinc dust (12 g.) in 70% acetic acid containing hydrochloric acid (3 drops of 10N.) for 0·5 hour. (*c*) Its solution in ethanol (40 ml.) mixed with amalgamated zinc dust (10 g.) with periodic addition of hydrochloric acid (20 ml. of 10N.) over 2 hours, the temperature being kept below 15°, and finally, hydrolysis of the crude product with alkali. In all cases, a high yield (90%) of 14-*hydroxydocosanoic acid* was obtained. Crystallisation from acetone furnished the hydroxy-acid in colourless prisms, m. p. 90°, depressed to 78—82° by admixture with the 13-isomer (Found: C, 73·9; H, 12·5. $C_{22}H_{44}O_3$ requires C, 74·2; H, 12·3%).

A sample was oxidised in warm acetic acid solution with chromic acid (20N.) to give the 14-ketodocosanoic acid which separated from aqueous alcohol in plates, m. p. 85°. A mixture of this keto-acid and a sample of 14-ketodocosanoic acid, m. p. 83° (prepared from behenolic acid and sulphuric acid), melted at 83—84°.

Aluminium isopropoxide. The crude keto-methoxy-acid (26 g.) was added to *iso*propanol (250 ml.) in which aluminium (4·5 g.) had been dissolved, and the mixture slowly distilled through the Fenske column until the distillate was free from acetone (7 hours). Treatment of the residue with warm dilute sulphuric acid (1 l. of N.) until decomposition of the aluminium complex was complete afforded an oil which solidified and was collected by filtration. By crystallisation from light petroleum (b. p. 40—60°) at room temperature and at 0°, it was separated into a yellow, viscous oil (A) and solid 13-*hydroxy*-14-*methoxydocosanoic acid* (B) in the form of colourless prisms, m. p. 50—51° (Found: C, 71·4; H, 11·6. $C_{23}H_{46}O_4$ requires C, 71·5; H, 11·9%).

Brassidic and Erucic Acids.—(*a*) The foregoing oily reduction product (A; 6 g.) was dissolved in toluene (100 ml.), and the solution saturated with dry hydrogen bromide and left overnight. The mixture was then heated to 80° and kept at this temperature with passage of hydrogen bromide for 6 hours. The oil, obtained after removal of solvent, was dissolved in ethanol (25 ml.), and the solution added to zinc dust (10 g.). The mixture was boiled under reflux with periodic addition of alcoholic hydrogen chloride (5 ml. of 4N. in all) for 3 hours. Decantation of the solution from zinc and dilution with water furnished an oil which was isolated with benzene. The combined organic extracts were washed with aqueous sodium hydrogen carbonate and distilled to give, after a small fore-run, an unsaturated ester, b. p. 178—182°/0·3 mm., n_D^{20} 1·4530 (3 g.). Hydrolysis of the latter with aqueous alcoholic sodium hydroxide afforded a crude acid, m. p. *ca.* 50°, which was dissolved in boiling ethanol (9 ml.). Cooling of this solution to 20° gave crop (A) (1·2 g.), to 0° crop (B) (0·2 g.), and to −50° crop (C) (0·15 g.). Crop (A) had m. p. 60° and was substantially pure brassidic acid; it separated from ethanol in colourless, lustrous plates, m. p. 60·5°, undepressed by admixture with authentic material (Found: C, 77·8; H, 12·4. Calc. for $C_{22}H_{42}O_2$: C, 78·1; H, 12·4%). It furnished a *p*-bromophenacyl ester which crystallised from ethanol in plates, m. p. 74,° undepressed by admixture with authentic material, and gave, on treatment with peracetic acid (Dorée and Pepper, *loc. cit.*), the corresponding dihydroxybehenic acid, m. p. and mixed m. p. 131°. Crop (B) was a mixture of (A) and (C) and was not investigated further. Crop (C) (m. p. 28—30°) was dissolved in ethanol (5 ml.), and excess of aqueous lithium hydroxide added at the b. p. On cooling, the beautifully crystalline lithium salt of erucic acid (150 mg.) separated. Decomposition with acid in the presence of light petroleum (b. p. 40—60°) furnished almost pure erucic acid (85 mg.) (Found: equiv., 337. Calc. for $C_{22}H_{42}O_2$: equiv., 338), m. p. 31°, raised to 31—32° by admixture with a specimen of the natural material. It formed a *p*-bromophenacyl ester, m. p. 62°, and a dihydroxybehenic acid, m. p. 98°, both undepressed by admixture with samples prepared from the natural material.

(*b*) A stream of hydrogen bromide was passed through the molten 13-hydroxy-14-methoxydocosanoic acid (B) (1·2 g.) at 150—160° for 6 hours. The residue was treated with ethanol and zinc as before and, in view of the small quantity available, was hydrolysed directly with alkali to give crude brassidic acid (0·4 g.), m. p. 58—59°. Crystallisation from ethanol furnished pure brassidic acid in plates, m. p. 60°, undepressed by authentic material.

BIRKBECK COLLEGE, LONDON, E.C.4.

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40. *Electrolytic Dissociation Processes. Part VI. The Dielectric Polarisation of Iodine Cyanide and the Ionisation of the Cyanogen Halides.*

By FRED FAIRBROTHER.

Iodine cyanide undergoes a polarisation in an electron-donor solvent, similar to that shown by molecular iodine. Measurements have been made of its dielectric polarisation in carbon tetrachloride, benzene, di*iso*butylene, and dioxan, and of the ultra-violet light absorption in carbon tetrachloride, di*iso*butylene, and dioxan. The behaviour of the cyanohalogens as halides or as cyanides is due, not to differences in type of bonding, but to differences in solvent-solute interaction in a basic solvent and to the energy relationships involved in ionisation and in the particular reactions.

THE observation that the homopolar valency bond in molecular iodine becomes polarised on dissolution of the iodine in a medium which possesses some basic or electron-donor character, even though of low dielectric constant, such as dioxan, benzene, *p*-xylene, or an olefin (Fairbrother, this series, Part V, *J.*, 1948, 1051) suggested that a similar phenomenon might be observed with iodine cyanide, especially if the structure implied by this name, *i.e.*, I^+CN^- made a substantial contribution to the structure of the molecule. The chemical reactions of an aqueous solution of this compound give support to this possibility. Even the usual method of preparation from molecular iodine and an alkali cyanide, *viz.*, $I_2 + CN^- \rightleftharpoons ICN + I^-$, a reaction which is reversed in acid solution, suggests that it is formed in the first place by the union of a cyanide ion with a positive univalent iodine cation stabilised in alkaline solution by the electron-donor hydroxyl ions.

The dielectric polarisation of ICN has now been measured in carbon tetrachloride, benzene, di*iso*butylene, and dioxan, in which, if we assume an electronic polarisation of 19·0 c.c. and neglect the unknown atomic polarisation, the dipole moments are respectively 3·64, 3·76, 4·01, and 4·40 D. In none of these solvents did ICN exhibit appreciable conductivity.

The experimental data are recorded in the following tables, in which w_2 is the weight fraction of solute, f_2 the mol.-fraction of solute, ε the dielectric constant, d_4^{25} the density, and P_2 the molar solute polarisation.

ICN in carbon tetrachloride.

$w_2 \times 10^6$.	f_2.	ε.	d_4^{25}.	P_2 (c.c.).
0	0·000	2·2268	1·5847	—
1469	0·001477	2·2510	1·5851	288
1549	0·001558	2·2526	1·5854	289
2071	0·002090	2·2619	1·5856	292
2698	0·002713	2·2727	1·5860	292
3226	0·003235	2·2828	1·5863	297
			Average	292

$P_0 = 273 \pm 2$ c.c.; $\mu = 3{\cdot}64$ D.

ICN in di*iso*butylene.

$w_2 \times 10^6$.	f_2.	ε.	d_4^{25}.	P_2 (c.c.).
0	0·000	2·0891	0·7134	—
3589	0·002635	2·1206	0·7151	353
3723	0·002733	2·1218	0·7153	350
4393	0·003227	2·1276	0·7156	351
5334	0·003919	2·1364	0·7162	352
			Average	351·5

$P_0 = 332{\cdot}5 \pm 1$ c.c.; $\mu = 4{\cdot}01$ D.

ICN in benzene.

$w_2 \times 10^6$.	f_2.	ε.	d_4^{25}.	P_2 (c.c.).
0	0·000	2·2727	0·8732	—
8,222	0·004216	2·3577	0·8780	308
12,852	0·006605	2·4082	0·8804	311
14,056	0·007228	2·4219	0·8813	311
24,462	0·01264	2·5423	0·8874	312
24,584	0·01271	2·5454	0·8877	313
			Average	311

$P_0 = 292 \pm 1$ c.c.; $\mu = 3{\cdot}76$ D.

ICN in dioxan.

$w_2 \times 10^6$.	f_2.	ε.	d_4^{25}.	P_2 (c.c.).
0	0·000	2·2124	1·0275	—
11,934	0·006910	2·4062	1·0351	404
13,275	0·007690	2·4250	1·0358	398
16,355	0·009487	2·4784	1·0378	398
20,558	0·01195	2·5458	1·0404	391
21,572	0·01254	2·5639	1·0411	391
28,664	0·01671	2·6970	1·0457	379
30,563	0·01780	2·7097	1·0469	377

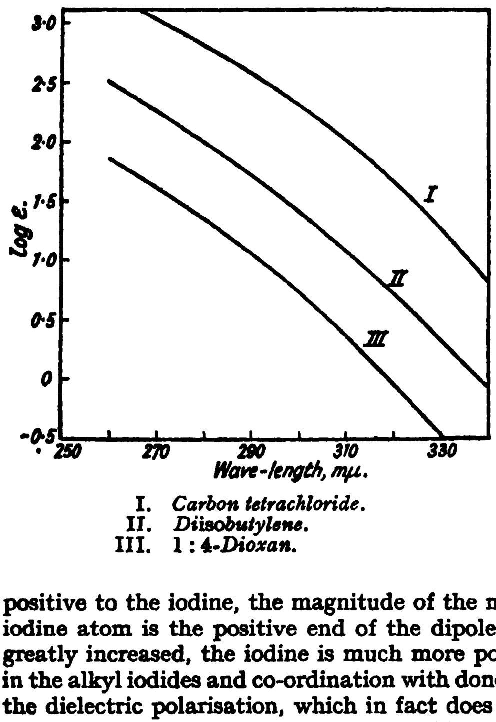
${}_{\infty}P_2 = 420$ c.c.; ${}_{\infty}P_0 = 401$ c.c.; $\mu = 4{\cdot}40$ D.

The polarisations and moments have been calculated by the usual Clausius–Mosotti–Debye method. Only in dioxan was there any noticeable change of polarisation with concentration, and in this the molar solute polarisations were extrapolated to infinite dilution against the weight fraction w_2; in the remaining solvents the polarisations were averaged. The extrapolation to infinite dilution of the dielectric constants and densities of the solutions, with a view to using the respective intercepts as solvent parameters (cf. Halverstadt and Kumler, *J. Amer. Chem. Soc.*, 1942, **64**, 2988), gave results which were not significantly different from measurements on the pure solvents, which were therefore used in the calculations. A single large sample (2—3 l.) of each solvent was used for all measurements and kept throughout with its vapour in contact with anhydrous magnesium perchlorate (Fairbrother, *J.*, 1945, 503). Cryoscopic measurements in benzene by Zappi (*Bull. Soc. chim.*, 1930, **47**, 453) and distribution measurements between water and carbon tetrachloride by Yost and Stone (*J. Amer. Chem. Soc.* 1933, **55**, 1889) indicate a normal molecular weight for ICN in these solvents; we may presume the like for the remaining two.

There do not appear to be any recorded measurements of the dielectric polarisations of ICN in the vapour state. Zwartsenberg and Ketelaar (*Rec. Trav. chim.*, 1942, **61**, 877) have measured the dipole moment in benzene solution, which solvent they state " was chosen because solutions in other solvents showed a considerable electrical conductivity." They obtained a value of $\mu = 3{\cdot}82$ D. by the usual Debye method, neglecting atomic polarisation, or $\mu = 3{\cdot}77$ D. assuming an atomic polarisation of 8·3 c.c., which was derived as the mean of the atomic polarisation in molecular iodine and in molecular cyanogen. This method of averaging P_A however, implies an additive character which is not strictly justifiable, and in the absence of direct evidence, the atomic polarisation of ICN must be regarded as an unknown quantity.

For comparison, therefore, the dipole moments in the several solvents have been calculated with the neglect of atomic polarisation, inclusion of which may reduce the moments given by something under 0·05 Debye unit. The electronic polarisation (Na_D) has been taken as 19·0 c.c. On the one hand, the sum of the partial refractivities of covalently bonded iodine (Eisenlohr, *Z. physikal. Chem.*, 1911, **75**, 585) and of CN derived from the molar refractivity of HCN (Watson and Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144) is (13·90 + 5·16) = 19·06 c.c., whilst direct determinations of the refractivity, for Na_D, give 19·00 ± 0·05 c.c. in benzene (Zwartsenberg and Ketelaar, *loc. cit.*) and a mean of 19·10 c.c. in alcohol and chloroform (Zappi, *Bull. Soc. chim.*, 1930, **47**, 537).

It may be observed that dissolution of ICN in the electron-donor solvents causes a significant increase in dielectric polarisation; in dioxan it is over 40% greater than in carbon tetrachloride. ICN is very freely soluble in dioxan but only about 0·5 g. dissolves in 100 g. of carbon tetrachloride. It may also be observed that, as with molecular iodine, the π electrons of the ethylenic bond in di*iso*butylene are more effective in bringing about the polarisation than the aromatic electrons of benzene.



I. *Carbon tetrachloride.*
II. *Diisobutylene.*
III. 1 : 4-*Dioxan.*

Further evidence of solvent–solute interaction is provided by the ultra-violet light absorption of ICN in these solvents. In the case of molecular iodine the shift in the absorption on dissolution in a donor solvent is apparent to the unaided eye; iodine cyanide absorbs only in the ultra-violet.

The ultra-violet light absorption of ICN and BrCN in ethanol and chloroform was studied by Gillam (*Trans. Faraday Soc.*, 1933, **29**, 1132), who found that the absorption curve of ICN, which discloses no maximum down to 240 mμ. is displaced towards the shorter wave-lengths in ethanol as compared with chloroform. There was no evidence of a similar shift in BrCN.

The ultra-violet light absorption of solutions of ICN in carbon tetrachloride, di*iso*butylene, and dioxan has now been measured by a Beckman photoelectric spectrophotometer. The absorption curves (see figure) show a marked displacement towards the shorter wave-lengths in the electron-donor solvents.

Since the bond moment of –CN in the alkyl cyanides is >3 D., the carbon being positive to the nitrogen, whilst the bond moment of –I in the alkyl iodides is $\sim$1·5 D., the carbon being positive to the iodine, the magnitude of the moment of ICN suggests that in this molecule the iodine atom is the positive end of the dipole. In ICN, therefore, unless the –CN moment is greatly increased, the iodine is much more positive (or less negative) towards the carbon than in the alkyl iodides and co-ordination with donor solvent molecules would be expected to increase the dielectric polarisation, which in fact does occur.

This is further supported by a consideration of the interatomic distances in ICN. These have recently been measured very accurately by Smith, Ring, Smith, and Gordy (*Physical Rev.*, 1948, **74**, 370) by a micro-wave technique. They find the C–I internuclear separation to be 1·995 A., which is considerably shorter than the separation in methyl iodide, 2·139 A. (Gordy, Simmons, and Smith, *ibid.*, p. 243). This they attribute "largely to resonance between the electronic structures $\overset{+}{\text{X}}{=}\text{C}{=}\overset{-}{\text{N}}$ and X–C≡N which gives the X–C bond some double character."

It is probable that in all the so-called cyanogen halides, the halogen atom is the positive end of the dipole of the gaseous molecule, with a decrease in moment ICN > BrCN > ClCN. There is experimental evidence of the smaller dipole moment of the bromide in benzene solution, 3·13 D. as compared with 3·82 D. (Zwartsenberg, *Rec. Trav. chim.*, 1943, **62**, 148).

The nature of the valency bonds in iodine cyanide and other cyanohalogens has given rise to much discussion (cf. Gmelin, " Handb. anorg. Chem.," 8th Edn., Berlin, 1933, No. 8, p. 457), chiefly based upon their chemical reactions, which have been studied by a number of workers and have led to conflicting theories.

Iodine cyanide is essentially an oxidising agent in aqueous solution, being unaffected by other oxidising agents and giving, when reduced, either free iodine or iodide ion according to the strength and excess of the reducing agent, *e.g.*, $2ICN + H_2SO_3 + H_2O = 2HCN + H_2SO_4 + 2HI$ (Chattaway and Wadmore, *J.*, 1902, **81**, 191) and $ICN + AsO_3^{3-} + 2OH^- = CN^- + AsO_4^{3-} + I^- + H_2O$ (Gutman, *Z. anal. Chem.*, 1924, **65**, 246), iodine being liberated in each case if the ICN is in excess.

If a solution of ICN in carbon tetrachloride or benzene is shaken with an aqueous solution of ferrous sulphate, the organic solvent slowly takes on the characteristic colour of free iodine. An aqueous solution is apparently unaffected by dilute sulphuric acid, but if it is made slightly alkaline and allowed to stand a few moments, on acidification free iodine is separated. Similarly, if pyridine is added to an aqueous solution, a yellow colour quickly develops and again iodine is precipitated on acidification. These latter reactions are presumably due to the formation of iodide and iodate from the unstable IOH or PyIOH respectively, and the subsequent oxidation of the iodide ion by the iodate on acidification. It is to such formation of iodide that the few reactions reported in which ICN behaves as an iodide are doubtless due. Thus, Normand and Cumming (*J.*, 1912, **101**, 1852) report that an aqueous solution of silver acetate very slowly gave a precipitate which was a mixture of silver cyanide, iodide, and iodate and that, when potassium hydroxide was added to the original solution, a copious precipitate of silver iodide appeared.

The reactions of ICN are essentially those of a cyanide of positive iodine : ClCN in contrast behaves as a chloride of cyanogen.

Zappi (*loc. cit.*, p. 453) has pointed out a number of differences between the reactions of ICN and ClCN : that silver nitrate does not react, or reacts very feebly, with ICN dissolved in water, alcohol, ether, or chloroform, but that ClCN slowly reacts, all the chlorine being ultimately precipitated after the lapse of 2—3 hours; that ICN is completely dissociated in (halogen)-acid solution, $ICN + HI = I_2 + HCN$, and (on gentle warming) $ICN + HCl = HCN + ICl$; that ICN gives iodate with potassium hydroxide (as observed by Nef, *Annalen*, 1895, **287**, 316) and a quantitative yield of iodine with potassium iodide, the cyanogen in both cases appearing as potassium cyanide, but that ClCN does not give chlorate or cyanide with potassium hydroxide, or chlorine with HCl; that whilst a ferrous–ferric mixture gives an abundant cyanide reaction with ICN, it gives a completely negative result with ClCN. (It may be noted that the Prussian-blue test is not given on addition of a solution of ICN to one containing ferrous and ferric salts unless it is first made alkaline and subsequently acidified.) Zappi concluded that such facts seem to indicate a difference in constitution between the two compounds.

Striking as these differences in reaction are, they do not, however, form conclusive evidence that there is any fundamental difference *in kind* between the valency bonds in ClCN and in ICN. Indeed, the physical evidence indicates otherwise. Badger and Woo (*J. Amer. Chem. Soc.*, 1931, **53**, 2573) found that the ultra-violet absorption was of the same type for ClCN, BrCN, and ICN, and West and Farnsworth (*J. Chem. Physics*, 1933, **1**, 402) showed that the Raman spectrum of all three compounds is similar.

The manner in which a given molecule will ionise is not a unique function of the structure of the molecule itself, but also of its environment; this behaviour is familiar as amphoteric reaction in acid–base systems.

Consider the alternative modes of ionisation of ClCN and ICN in a pure solvent. The energies involved in the ionisation and subsequent electrolytic dissociation may be divided into the following steps :

(A) Formation of halide anions and cyanogen cations :

$$e.g., \mathrm{ICN} \xrightarrow{a} \mathrm{I_g} + \mathrm{CN_g} \xrightarrow{b} \mathrm{I_g^-} + \mathrm{CN_g^+} \xrightarrow{c} \mathrm{I_s^-} + \mathrm{CN_s^+}$$

(*a*) Energy of dissociation of dissolved ICN to $I_g + CN_g$.
(*b*) Ionisation potential of $CN_g \longrightarrow CN_g^+$ – electron affinity of $I_g \longrightarrow I_g^-$.
(*c*) Sum of solvation energies of CN_g^+ and I_g^-.

(B) Formation of halide cations and cyanogen anions :

$$e.g., \mathrm{ICN} \xrightarrow{a'} \mathrm{I_g} + \mathrm{CH_g} \xrightarrow{b'} \mathrm{I_g^+} + \mathrm{CN_g^-} \xrightarrow{c'} \mathrm{I_s^+} + \mathrm{CN_s^-}$$

(*a′*) Energy of dissociation of dissolved ICN to $I_g + CN_g$.
(*b′*) Ionisation potential of $I_g \longrightarrow I_g^+$ – electron affinity of $CN_g \longrightarrow CN_g^-$.
(*c′*) Sum of solvation energies of I_g^+ and CN_g^-.

Since a and a' are the same, the course of the ionisation is determined by whether $(c - b)$ or $(c' - b')$ is the greater. In NaCN and KCN, which have a rock-salt structure at room temperature, the CN^- ion is believed to achieve spherical symmetry by rotation. The edge of the unit cell in KCN is closely similar to that in KBr, so that the rotating CN^- ion must have an effective radius which is close to that of the Br^- ion (cf. Verweel and Bijvoet, *Z. Krist.*, 1938, **100**, 201; and W. G. Palmer, "Valency," Cambridge, 1944, p. 54). It seems probable, therefore, that the ionisation potential and electron affinity of the cyanogen radical may also be similar to those of the bromine atom. The chlorine atom, however, is very much smaller than the iodine atom, its ionisation potential is 2·35 volts greater and its electron affinity 0·53 volt greater than those of iodine.

Consequently, whilst the ionisation of ClCN into Cl^+ and CN^- may be much more endothermic than into $^-$ Cl and CN^+, the ionisation of ICN into I^+ and CN^- may be less difficult than into I^- and CN^+. The differences in heats of solvation of the ions in the respective alternatives would be insufficient to overcome the difference in endothermicity in the case of ClCN. It follows, therefore, that there should be few if any reactions in which ClCN behaves as a cyanide, but a number in which the energies of solvation or reaction of the resulting ions will be sufficient to bring about the ionisation and reaction of ICN as a cyanide.

In computing the energies of solvation of the cations, it is necessary to take into account not only the electrostatic energy of solvation in a chemically indifferent medium, but also the possibility of bond formation between solvent and solute molecules. This will be especially significant in basic, or electron-donor solvents, which are able to form a co-ordinate bond with a halogen cation.

It would appear that water in itself is not sufficiently basic to bring about the appreciable ionisation of ICN, as shown by the lack of reaction with silver nitrate. This, however, may occur in a much more basic solvent or in aqueous solution in the presence of a strongly electron-donor solute species such as hydroxyl ion.

Clark and Streight (*Trans. Roy. Soc. Canada*, 1928, **22**, [3], 323) report that electrolysis of 0·1M-solutions of ICN in a number of carefully dried organic solvents, acetamide, benzene, acetonitrile, nitrobenzene, methanol, ethanol, nitromethane, aniline, and quinoline, gave iodine at the *anode* and cyanide or cyanogen or paracyanogen at the cathode, but that solutions in pyridine gave iodine at the *cathode* and cyanide at the anode, and that on addition of water iodine again appeared at the anode. It is probable, however, that the last observation was due to the secondary decomposition into iodide and iodate as described above.

The electrical conductivity of iodine cyanide in pyridine was studied carefully by Audrieth and Birr (*J. Amer. Chem. Soc.*, 1933, **55**, 668), who found that it increases with time to give maximum values. The experimental evidence indicated that the reaction between solvent and solute resulted in the primary formation of a non-conducting addition compound which in time changes over into a true quaternary pyridinium salt, 1-iodopyridinium cyanide. A similar mechanism the formation of 1-iodopyridinium iodide would account for the conductivity of molecular iodine in pyridine.

This reaction of pyridine and its stabilising effect on the positive iodine is paralleled by its behaviour in stabilising the univalent iodine cation in the salts prepared by Carlsohn (*Angew. Chem.*, 1932, **45**, 580; 1933, **46**, 747) and by the abnormal positive heat of solution of iodine in pyridine. Heats of solution of iodine in a variety of solvents have recently been measured accurately by Hartley and Skinner (to be published); they find that whereas in hydrocarbons and a number of oxygen-containing solvents, the heat of solution of iodine is negative, yet in pyridine it is positive. A simple test-tube experiment shows that the heat of dissolution of ICN in pyridine is also positive.

BrCN, which occupies an intermediate position, is stated to be un-ionised in water, neutral to litmus, and to give no precipitate with silver nitrate solution. It is soluble in cold concentrated sulphuric, hydrochloric, or nitric acid without decomposition, but is instantly hydrolysed by aqueous alkali hydroxides or carbonates into cyanide, bromide, and bromate; bicarbonates have no action (Williams, "Cyanogen Compounds," London, 1948, 9). Its ultra-violet light absorption (Gillam, *loc. cit.*) shows that there is much less solvent–solute interaction in ethanol than in the case of ICN. Clark and Streight (*loc. cit.*), using Sampey's method (*J. Amer. Chem. Soc.*, 1927, **49**, 2849) for the quantitative determination of positive halogen by titration with stannous chloride, report that BrCN repeatedly titrated as if it contained 89·2% of positive bromine, whilst iodocyanogen gave results corresponding to 99% of positive iodine.

It is to be concluded, therefore, that the positive iodine cation does not pre-exist in the free

ICN molecule, but is formed as it is in molecular iodine, either by a solvolytic ionisation alone in a very basic solvent like pyridine, or in other solvents by the action of some strongly electron-donor species in solution such as the hydroxyl ion in its alkaline hydrolysis, and that the contrasting behaviour of ClCN is not due to any great difference in the electronic structures of the free molecules, but to differences of solvent–solute interaction and of the energies involved in the particular reactions.

EXPERIMENTAL.

Materials.—Iodine cyanide was prepared in the usual manner by the slow addition of iodine to concentrated aqueous potassium cyanide, followed by cooling in a refrigerator, filtration, washing and drying of the crystals. The crude product was purified by sublimation in a current of dry nitrogen, and samples were freshly re-sublimed at a comparatively low temperature immediately before each determination. The final product was snow-white.

Solvents.—Benzene (b. p. 80·1° ± 0·1°/762 mm.), dioxan (b. p. 100·2—100·6°/774 mm.), and di*iso*butylene (b. p. 101·0—102·5°/757 mm.) were purified as described in Part V (*J.*, 1948, 1051). (The di*iso*butylene boiled over a wider range and differed in both dielectric constant and density from that used in Part V, which was from a different source.) Carbon tetrachloride, "for medicinal purposes" (Allbright and Wilson), was dried by long contact with phosphoric oxide and fractionated through an efficient column in a stream of dry nitrogen; b. p. 76·4° ± 0·2°/762 mm.

Measurements.—Dielectric constants and densities were measured at 25·00° as previously described (Part IV, *J.*, 1945, 503).

I am indebted to Messrs. Imperial Chemical Industries Ltd. for a grant for the purchase of apparatus.

THE UNIVERSITY OF MANCHESTER. [*Received, August* 19*th*, 1949.]

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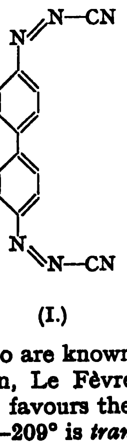
41. *The Isomerisation of Labile Diphenyl-4 : 4′-bisdiazocyanide in Solution.*

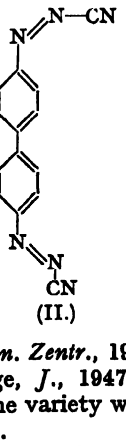
By D. D. BROWN, R. J. W. LE FÈVRE, and R. N. WHITTEM.

The two *known* isomers of the molecule named in the title are "*cis-cis-*" and "*trans-trans-*"; a third variety, "*cis-trans-*," should exist but is so far unknown. If the spontaneous formation of the stable from the unstable forms involved simultaneous configurational inversions, the situation would be explicable. However, the process is now found to proceed by a more complex mechanism. Whilst, in benzene solution, it appears to follow first-order kinetics with an activation energy of 26·9 kcals./g.-mol., in the polar solvents *o*-dichlorobenzene, pyridine, and nitrobenzene the reaction is not of the first order. The suggestion is therefore made that the reaction consists of two consecutive first-order inversions, with the "*cis-trans-*" compound as an intermediate. This requires the assumption that, in benzene solution, the rate of one of these inversions is not significant kinetically and that the overall change in this solvent is governed by only one of the two rates.

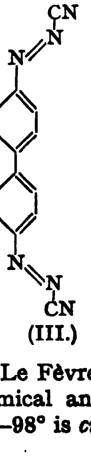
ON Hantzch's theories of the configuration of the $-\mathrm{N}{=}\mathrm{N}-$ group, diphenyl-4:4′-bisdiazocyanide should exist in three isomeric forms, (I), (II), and (III):



(I.)



(II.)



(III.)

In fact, only two are known (Euler, *Chem. Zentr.*, 1907, i, 1572; Le Fèvre and Vine, *J.*, 1938, 1878; Anderson, Le Fèvre, and Savage, *J.*, 1947, 445). Chemical and physical evidence (Le Fèvre *et al.*) favours the view that the variety with m. p. 97—98° is *cis-cis-* (I) whilst that with m. p. 208—209° is *trans-trans-* (III).

The *cis-trans*-species (II) remains, so far, unknown, notwithstanding the experimental fact that the spontaneous change of (I) into (III) proceeds quite slowly in the dissolved state (Le Fèvre and Vine, *loc. cit.*). In addition to the work already recorded by Le Fèvre and Northcott (this vol., p. 944) attention has therefore been directed to the kinetics of the production of (III) from (I) in a hope that indications concerning (II) might thereby be revealed.

At the outset there appeared three possibilities. These were: (*a*) that (I) passes directly into (III) by two simultaneous first-order reactions of equal velocities; (*b*) as (*a*) except that the velocities are unequal; and (*c*) that two consecutive first-order reactions $(\mathrm{I} \xrightarrow[k_1]{} \mathrm{II} \xrightarrow[k_2]{} \mathrm{III})$ are involved.

Case (*a*), if relevant, would explain the absence of isomer (II); it requires that (I) ⟶ (III) should appear to be of first order. One would predict that the activation energy needed in such a process is in the region of 46 kcals./g.-mol., *i.e.*, twice that required by each separate azo-inversion.

Case (*b*) seemed a reasonable contingency. As soon as the isomerisation commences, the environmental (polarisation and polarisability) factors for the second $-\mathrm{N}{=}\mathrm{N}-$ cannot be exactly as before. Each azo-group will be under a varying influence, from the other end of the molecule, during the actual act of inversion. Separate molecules, however, would behave similarly and the overall rate (as observed) should still be of the " first order."

Case (*c*) seemed the most likely mechanism. This would require the reacting molecules to possess, at any one time, only that activation energy necessary for one azo-inversion. If the quantity $e^{-E/RT}$ represents the probability of a molecule having energy in excess of E then the probability of a molecule having energy in excess of $2E$ will be roughly only $1/e^{40}$ of the first probability. The chance then, that a molecule will react by a consecutive mechanism would appear to be far greater than the chance of both azo-groups being inverted simultaneously.

To follow a consecutive reaction, involving three molecular species, by the variation of an additive physical property the concentrations of (I), (II), and (III) may be written in terms of A_1, the initial concentration of (I) and the two constants k_1 and k_2:

$$(C_{\mathrm{I}})_t = A_1 e^{-k_1 t}$$
$$(C_{\mathrm{II}})_t = A_1 k_1 (e^{-k_1 t} - e^{-k_2 t})/(k_2 - k_1)$$
$$(C_{\mathrm{III}})_t = A_1[1 - (k_2 e^{-k_1 t} - k_1 e^{-k_2 t})/(k_2 - k_1)]$$

The second equation has a maximum value dependent on the ratio $r = k_2/k_1$:

$$(C_{\mathrm{II}})\mathrm{max.} = [A_1 r/(1 - r)][e^{-r \ln r/(r-1)} - e^{-\ln r (r-1)}]$$

If the rate displaying property, X, is one which, for each solute separately in dilute solution, conforms to the equation: $X_{\mathrm{SI}} = X_{\mathrm{S}}(1 + \alpha w_1)$, where X_{S} refers to the solvent, X_{SI} refers to the solution of (I), and w_1 is the weight fraction of solute (I), and if the property is additive for a solution containing a mixture of the three solutes, such that:

$$X_{\mathrm{SI,II,III}} = X_{\mathrm{S}}(1 + \alpha w_1 + \beta w_2 + \delta w_3)$$

then it is obvious that, in the present problem, a graph of $X_{\mathrm{SI,II,III}}$ against time will be, in effect, the sum of three curves: an exponential decay curve, a growth curve, and a curve with an intermediate maximum.

The interpretation of such a graph would be rather limited. If X_{SII} were much greater than X_{SI} and X_{SIII} the curve might show a maximum or points of inflection. The presence of such characteristics would constitute strong evidence for the existence of an intermediate form. In their absence, the fact that the reaction was not of the first or the second order would remain the only evidence for a consecutive mechanism. It is relevant to note here that some consecutive reactions *appear* to be first-order reactions. This occurs when $k_1 \gg k_2$ or *vice versa*, but Walker (*Proc. Roy. Soc. Edinburgh*, **1898**, **22**, 23), and Mellor (" Chemical Statics and Dynamics," Longmans, 1904, Chapters V and VI) quote numerical examples to show that r needs to be greater than 100 to produce a passable semblance of constancy for k (first order) over all but the early stages of the reaction.

EXPERIMENTAL.

The 4 : 4′-diphenylbisdiazocyanides were found to be best prepared by the following slight modification of the directions of Anderson, Le Fèvre, and Savage (*loc. cit.*). The benzidine was first purified by several recrystallisations from alcohol, then converted (5 g. in 40 c.c. of EtOH) into the dihydrochloride by adding 10N-HCl (18 c.c.) to its hot solution, and bisdiazotised ($NaNO_2$, 3·9 g.; H_2O, 60 c.c.) at 5—10°. The clear resultant liquid was well stirred with chloroform, the whole cooled below −10° (carbon dioxide–alcohol), daylight excluded, and sodium cyanide (3 g. in the minimum amount of water) added. The heavy layer was then quickly separated, washed with water, and run into twice its volume of light petroleum at −30°.

The product, after rapid filtration, was dried, and stored *in vacuo* in the dark. The stable isomeride could be obtained by concentrating the filtrates after they had been kept for several days at room temperature.

Velocity measurements by the dielectric method were made difficult by the relative insolubility of the stable form causing, in most solvents, crystallisation to occur before the reaction had progressed a useful distance. To prevent this, initial concentrations were reduced, but the capacity changes were then so small that their accurate determination required apparatus with a high degree of frequency stability and temperature control. The dielectric-constant method was eventually abandoned in favour of a photometric method. For this latter method the Hilger Spekker-absorptiometer was used, the rate-displaying property being the change in the quantity of light absorbed by the solution from a narrow band of pre-selected wave-lengths. To enable a suitable light range to be chosen for each medium, spectral transmissivities of the two separate forms as solutes were first explored (see later), and of the filters supplied by the makers, those passing the band 5600—6100 A. used with benzene and those passing 4800—6200 A. for the other solvents.

In benzene, the maximum concentration that could be used was 0·06%. Crystallisation of the *trans-trans*-compound occurred at higher concentrations. The necessity for using such dilutions limited the accuracy of the measurements. Readings were taken by pouring 30 c.c. at a time from the main reaction flask (painted black to exclude all light) into a 4-cm. cell. The null point was observed at once, under a standard procedure, and with the shutter reset for the pure solvent before each reading. The logarithmic scale of the instrument was first calibrated for known mixtures of *cis-cis-* and *trans-trans*-forms. For benzene solutions, a linear relation was obtained between the scale reading and the concentration of *cis-cis-* in the presence of *trans-trans*-forms. Slight departures from linearity were found to exist in the calibration curves for the other solvents. Now, if at all times during the isomerisation only two molecular species were present, as would be the case in processes (*a*) and (*b*), the rate-displaying property chosen above could be used in determining the kinetics of the reaction. This would also apply to process (*c*) if $r > 100$. In the presence of a third molecular species there would be no way of relating scale reading to concentration and any attempt to obtain constant *k* values from either first- or second-order equations should fail. Such failure to obtain constant *k* values would be, in itself, evidence for a consecutive mechanism.

RESULTS.

Roughly, " half-change " times seem to be independent of the initial concentration (cf. Table I). However, despite this, in nitrobenzene (as also in pyridine or *o*-dichlorobenzene) the reaction is unlikely to be truly of the first order, since *k*, if appropriately evaluated for each observational time interval, is not constant (Table II) : On the other hand, in benzene, the values of *k*, if similarly calculated, do appear almost invariant, and lead to an apparent activation energy for the change of 26·9 kcals./g.-mol. These statements are illustrated in the figure. From these facts we draw the conclusions set out in the last two sentences of the " Summary" to this paper.

TABLE I.

Solvent.	Initial concn.	Temp.	Time for ½ change.
$C_6H_5{\cdot}NO_2$	5·4 g./litre	25°	9·5 hr.
,,	6·1	,,	8·9 ,,
,,	7·8	,,	9·0 ,,
C_6H_6	0·03 wt.-%	35	3·9 ,,
,,	0·03 ,,	,,	3·7 ,,
,,	0·05 ,,	,,	4·0 ,,
,,	0·03 ,,	25	18 ,,
,,	0·05 ,,	25	16 ,,

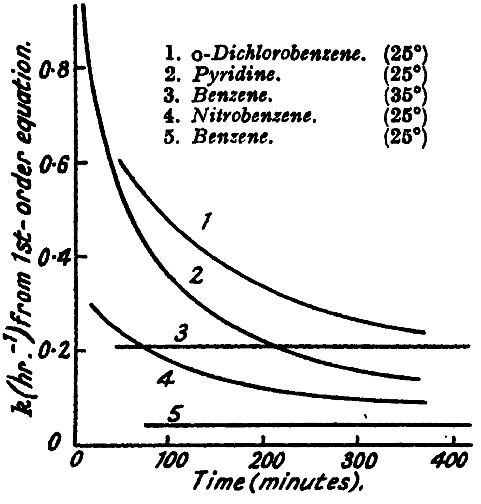
TABLE II.

Variation of k *with time.*

{*k* calculated from first order equation; $kt = \ln[a/(a - x)]$}.

$C_6H_5{\cdot}NO_2$.		Pyridine.		*o*-Dichlorbenzene.		Benzene.			
25°.		25°.		25°.		35°.		25°.	
Time, min.	*k*.	Time, min.	*k*.	Time, min.	*k*.	Time, min.	*k*.	Time, min.	*k*.
16	0·300	9	0·94	22	0·49	73	0·22	122	0·041
56	0·224	44	0·55	44	0·60	200	0·19	255	0·051
74	0·208	64	0·46	75	0·53	307	0·22	301	0·048
93	0·180	87	0·39	122	0·43	370	0·21	414	0·048
143	0·151	116	0·33	209	0·33			1267	0·040
171	0·137	189	0·23	309	0·26			2960	0·039
1289	0·057	1340	0·06	1361	0·16				

Visual Absorption Spectra of the Labile and Stable Forms.—For reasons explained by Le Fèvre and Wilson (this vol., p. 1106) when reporting the ultra-violet absorption spectra of isomeric pairs of benzenediazocyanides, we took the opportunity, during the process of filter selection (see above), to make qualitative comparisons of the absorbing properties of the two bisdiazocyanides of the present work towards visible light. Equivalent solutions (sometimes prepared directly and sometimes by allowing complete thermal change to occur in the dark) of various concentrations in *cyclo*hexanone or nitrobenzene were examined in the Hardy recording spectrophotometer. The wave-length range accessible covered only 4000—7000 A., and since in no cases have the automatic traces traversed an absorption peak they are not reproduced. For each pair of solutions, however, the following facts were consistently and definitely displayed: (*a*) the point at which 100% absorption ceased was further towards the red end of the spectrum for the stable form; and (*b*) the general slope of the %-transmittance–wave-length curves was slightly steeper for the unstable form. We are satisfied, therefore, that the type and degree of spectral differences (*i.e.*, of intensity and $\lambda_{max.}$), mentioned by Le Fèvre and Wilson (cf. also. Le Fèvre, Northcott, and Wilson, *Chem. and Ind.*, 1948, 732), occur also for the present cases. It is relevant to recall that in the solid states the stable variety is maroon-coloured, in contrast to its isomer, which is orange (Anderson, Le Fèvre, and Savage, *J.*, 1947, 451).



Financial assistance from the Commonwealth Science Fund is gratefully acknowledged.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA.

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42. *Some Amidines and Dihydroglyoxalines of the* 1 : 1-*Diphenylethane and* 1 : 1-*Diphenylpropane Series.*

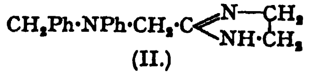
By J. O. JÍLEK and M. PROTIVA.

In view of the well-known similarity of the pharmacological properties between ethyldialkylamines and 2-methyldihydroglyoxaline derivatives 2-(2 : 2-*diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI) has been prepared as a glyoxaline analogue of " Aspasan " (V). Three similar amidines (VIII) and two lower homologues (IX and X) have also been prepared, one of them (VIII; R = H) exerting a relatively strong antihistaminic action.

DJERASSI and SCHOLZ (*J. Amer. Chem. Soc.*, 1947, 69, 1688) noticed the analogy between the known antihistaminic agents " Antergan " (I) and " Antistin " (II). (II) differs from (I) only in that the 2-methyldihydroglyoxaline group replaces the dimethylaminoethyl moiety.

$CH_2Ph\cdot NPh\cdot CH_2\cdot CH_2\cdot NMe_2$

(I.)

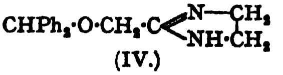

$CH_2Ph\cdot NPh\cdot CH_2\cdot C\begin{matrix}\nearrow N-CH_2\\ \searrow NH\cdot CH_2\end{matrix}$

(II.)

Making use of this analogy, these authors prepared a series of aryloxyacetamidines and 2-aryloxymethyldihydroglyoxalines and found them to show antihistaminic activity similar to that of the corresponding aryloxyethyldialkylamines. On the basis of the same assumptions the dihydroglyoxaline analogue (IV) of " Benadryl " (III) was recently prepared almost simultaneously in different laboratories (Protiva and Urban, *Coll. Trav. chim. Tchécosl.*, 1948, 13, 340; Cavallini and Mazzucchi, *Farmaco*, 1947, 2, 273; Dahlbom and Sjögren, *Acta Chem. Scand.*, 1947, 1, 777; Djerassi and Scholz, *J. Org. Chem.*, 1948, 13, 830) and was found to be quite similar to (III) in its pharmacological properties.

$CHPh_2\cdot O\cdot CH_2\cdot CH_2\cdot NMe_2$

(III.)

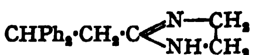

$CHPh_2\cdot O\cdot CH_2\cdot C\begin{matrix}\nearrow N-CH_2\\ \searrow NH\cdot CH_2\end{matrix}$

(IV.)

Considering these results, it seemed desirable to prepare amidine and dihydroglyoxaline analogues of 3 : 3-diphenylpropylamine derivatives, another pharmacologically interesting group characterised by " Aspasan " (V), showing antispasmodic and antihistaminic activity (Bockmühl and Ehrhart, *Annalen*, 1948, **561**, 52). Attention was paid first to the preparation

$CHPh_2{\cdot}CH_2{\cdot}CH_2{\cdot}N{<}[CH_2]_5$

(V.)



$CHPh_2{\cdot}CH_2{\cdot}C{\lessgtr}^{N—CH_2}_{NH{\cdot}CH_2}$

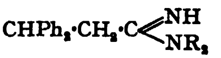
(VI.)

$Ph_2CH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$

(VII.)

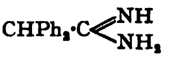
of 2-(2 : 2-*diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI), the analogue of " Aspasan " (V). This compound was obtained from ββ-diphenylpropionitrile either through *ethyl* ββ-*diphenylpropionimidate hydrochloride* by the method of Klarer and Urech (*Helv. Chim. Acta*, 1944, **27**, 1762), or by fusion with 2-aminoethylammonium toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497). The first method yielded an impure hydrochloride, which by the action of ammonia gave the base (VI), m. p. 101°. From the base a crystalline *hydrochloride* (m. p. 88—90°) and *picrate* were prepared. By the second method, a crystalline *toluene*-p-*sulphonate* was obtained, which could be converted into the base and hydrochloride, identical with the products obtained by other route. The base, toluene-*p*-sulphonate, and picrate gave good analytical results; the hydrochloride in contrast, even when thoroughly dried *in vacuo*, gave results which indicated that it was a monohydrate. Since, however, it might have been ββ-diphenylpropiono-2-aminoethylamide hydrochloride (VII), which could be formed by opening the glyoxaline ring of (VI), the *base* (VII) was prepared from ethyl ββ-diphenylpropionate by the action of excess of ethylenediamine at 210—220° (Hill and Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 822). The hydrochloride of (VII) melts at 214—215° and differs from that having m. p. 88—90°. The base (VII) is a solid of m. p. 118°.

Three new ββ-diphenylpropionamidines (VIII; $NR_2 = NH_2$, NMe_2 and $N{<}[CH_2]_5$) of a similar type were prepared by the action of an excess of ammonia or of the appropriate amine on ethyl ββ-diphenylpropionimidate hydrochloride. For comparison *diphenylacetamidine* (IX) and 2-benzhydryl-4 : 5-dihydroglyoxaline (X) were also prepared by standard methods.



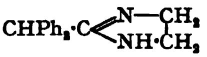
$CHPh_2{\cdot}CH_2{\cdot}C{\lessgtr}^{NH}_{NR_2}$

(VIII.)



$CHPh_2{\cdot}C{\lessgtr}^{NH}_{NH_2}$

(IX.)



$CHPh_2{\cdot}C{\lessgtr}^{N—CH_2}_{NH{\cdot}CH_2}$

(X.)

The soluble derivatives of compounds (VI), (VIII), (IX), and (X) were tested for antihistamine activity. Only the hydrochloride of (VIII; R = H) was found to be approximately equal in activity to " Aspasan " (0·1 unit of " Benadryl " activity). Further testing for antispasmodic, analgesic, and pressor activity is in progress.

EXPERIMENTAL.

M.p.s are corrected. Analytical samples were dried at 0·2 mm. (P_2O_5) for 10 hours at suitable temperatures. Semimicro-analyses were by Miss Bruchalová, Ing. Mňouček, Dr. Králíčková, and Ing. Rýpar.

ββ-Diphenylpropionitrile.—This was prepared from α-cyano-ββ-diphenylpropionic acid by the method of Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 338) and purified by distillation *in vacuo* (Freeman, Ringk, and Spoerri, *J. Amer. Chem. Soc.*, 1947, **69**, 858) and by crystallisation from ethyl alcohol–light petroleum. Yield 72%. B. p. 175—178°/2 mm. M. p. 88·5°.

Ethyl ββ-Diphenylpropionimidate Hydrochloride.—A solution of the above nitrile (11·7 g.) in a mixture of chloroform (60 c.c.) and absolute ethyl alcohol (7·5 c.c.) was saturated with dry hydrogen chloride at 0° and set aside for 10 days in a closed flask at 20°. After removal of the solvents at 30° *in vacuo* a crystalline residue remained, representing the crude product of m. p. 128°, in quantitative yield.

2-(2 : 2-*Diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI).—(*a*) The above imidate hydrochloride (8·8 g.), absolute ethylenediamine (1·9 g.), and absolute ethyl alcohol (50 c.c.) were refluxed for 7 hours in a slow stream of dry air in a bath at 100—115°. After cooling, the solution was filtered from ethylenediamine dihydrochloride [0·1 g.; m. p. 335—338° (decomp.)] which separated. The filtrate was concentrated under reduced pressure, the oily residue dissolved in water (70 c.c.), and the solution filtered and treated with concentrated aqueous ammonia (7 c.c.). The *base* (4·4 g.) was filtered off and recrystallised from 50% ethyl alcohol. It had m. p. 84—86°, or, after drying (P_2O_5 *in vacuo*), m. p. 101° (Found: C, 81·2; H, 7·5. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·2%). In another similar experiment the crude oily hydrochloride was dissolved in acetone (10 c.c.) and the solution treated with absolute ether (10 c.c.). The oil which separated crystallised (7·5 g.). Crystallisation from acetone raised the m. p. of the *hydrate* to 88—90° (Found: N, 9·2; Cl, 11·8. $C_{17}H_{19}N_2Cl,H_2O$ requires N, 9·2; Cl, 11·6%). The *picrate* crystallised from ethyl alcohol and melted at 168—170° (Found: C, 57·8; H, 4·9. $C_{23}H_{21}O_7N_5$ requires C, 57·6; H, 4·4%).

(*b*) A mixture of ββ-diphenylpropionitrile (35·0 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (39·2 g.) (m. p. 122—124°; Oxley and Short, *loc. cit.*) was heated for 3 hours at 200°. After cooling, the solidified mass was recrystallised from aqueous ethyl alcohol. The yield of *toluene*-p-*sulphonate*, m. p. 170—174°, was 92·5% (Found: C, 68·5; H, 6·5; N, 6·7. $C_{24}H_{26}O_3N_2S$ requires C, 68·2; H, 6·2; N, 6·6%). A suspension of this salt (15·0 g.) in hot water was treated with 20% sodium hydroxide

(30 c.c.) and extracted with chloroform. After evaporation of the solvent the residue crystallised (7·8 g.). After recrystallisation from acetone, the m. p. was 102° (Found: N, 11·3%). This base (2·0 g.) in acetone (2 c.c.) was treated with 23% alcoholic hydrogen chloride solution (1·2 c.c.). Recrystallisation of the crude product from acetone gave the hydrated hydrochloride, m. p. 88—90° (Found: C, 66·9; H, 7·0; N, 9·1%), whence the base, m. p. 100·5°, could be regenerated.

Ethyl ββ-Diphenylpropionate.—This was prepared from the nitrile by application of Spiegel's method (*Ber.*, 1918, **51**, 296). Diphenylpropionitrile (8·0 g.), absolute ethyl alcohol (7 c.c.), and concentrated sulphuric acid (2·0 c.c.) were refluxed for 3 hours at 120—130° (bath). Ethyl alcohol was distilled off *in vacuo* and the residue mixed with water (100 c.c.). The oil which separated was extracted with ether, and the solution was dried and evaporated. The residue distilled from a Hickman flask at 138—141°/0·25 mm. (yield, 5·5 g.). Wislicenus and Eble (*Ber.*, 1917, **50**, 253) gave b. p. 190—193°/12 mm.

ββ-Diphenylpropiono-2-aminoethylamide (VII).—The above ester (5·5 g.) and absolute ethylenediamine (6·0 c.c.) were heated in a sealed tube for 18 hours at 210—230°. After cooling, the excess of diamine was distilled off and the residual oil transformed (in ethyl alcohol solution) into the *hydrochloride*. Crystallisation from ethyl alcohol gave 2·0 g. of the product, m. p. 214—215° (Found: N, 9·5; Cl, 11·7. $C_{17}H_{21}ON_2Cl$ requires N, 9·2; Cl, 11·6%). From aqueous solution of this the *base* was obtained by treatment with 40% aqueous sodium hydroxide. Recrystallisation from benzene gave white prisms, m. p. 118° (Found: N, 10·6. $C_{17}H_{20}ON_2$ requires N, 10·4%).

ββ-Diphenylpropionamidine (VIII; R = H).—To a suspension of the crude imidate hydrochloride (prepared from 4·5 g. of nitrile) in absolute ethyl alcohol (10 c.c.), 8% absolute ethyl-alcoholic ammonia (100 c.c.) was added and the mixture was shaken in a closed flask for 3 hours at 20°. After 12 hours, shaking was repeated for a further 2 hours. Ammonium chloride, which separated, was filtered off and the filtrate evaporated *in vacuo* at 30—35° (bath). The residue was dissolved in chloroform (30 c.c.), the solution washed with water, 10% sodium hydroxide solution, and water, and the chloroform was distilled off. The oily residue (5·2 g.) is the crude base (VIII; R = H). The *picrate*, after recrystallisation from absolute ethyl alcohol, melted at 209—209·5° (Found: C, 55·8; H, 4·0; N, 15·5. $C_{21}H_{19}O_7N_5$ requires C, 55·6; H, 4·2; N, 15·5%).

NN-*Dimethyl-ββ-diphenylpropionamidine* (VIII; R = Me).—The crude imidate hydrochloride (4·5 g.) was dissolved in ethyl alcohol (20 c.c.), 18% ethyl-alcoholic dimethylamine solution (4·5 c.c.) was added and the mixture was set aside for 24 hours at room temperature. After evaporation of alcohol the residue was recrystallised from ethyl alcohol–ether. 3·2 G. of *hydrochloride*, m. p. 249°, were obtained (Found: C, 70·5; H, 7·3; N, 9·5. $C_{17}H_{21}N_2Cl$ requires C, 70·7; H, 7·3; N, 9·7%).

NN-*Pentamethylene-ββ-diphenylpropionamidine* (VIII; $NR_2 = N<[CH_2]_5$).—To the solution of crude imidate hydrochloride (6·2 g.) in absolute ethyl alcohol (30 c.c.) piperidine (2·0 g.) was added and the mixture set aside for 12 hours at room temperature. It was then evaporated *in vacuo* to dryness and gave, as above, 4·2 g. of *hydrochloride*, m. p. 250° (Found: C, 73·1; H, 7·6. $C_{20}H_{25}N_2Cl$ requires C, 73·0; H, 7·7%).

Ethyl Diphenylacetimidate Hydrochloride.—A solution of diphenylacetonitrile (6·6 g.), m. p. 74°, prepared by dehydration of diphenylacetamide (Neure, *Annalen*, 1889, **250**, 142), in a mixture of chloroform (30 c.c.) and absolute ethyl alcohol (5·0 c.c.) was saturated with hydrogen chloride at 0° and set aside for 14 days at room temperature in a closed flask. After evaporation of the solvents a crude product suitable for the preparation of the amidine was obtained.

Diphenylacetamidine (IX).—(*a*) A suspension of the above imidate hydrochloride in absolute ethyl alcohol (20 c.c.) was mixed with 8% ethyl-alcoholic ammonia (18·5 c.c.), and the mixture shaken for 2 hours at 20°. After 12 hours, shaking was repeated for an hour. Ammonium chloride was filtered off and the filtrate evaporated under reduced pressure. The remaining oil was dissolved in chloroform (50 c.c.), the solution washed with 5N-sodium hydroxide and water, and the chloroform evaporated. The residue is the crude amidine, m. p. 95—97° (7·1 g.). It gave a *picrate* which after recrystallisation from ethyl alcohol melted at 224—225° (decomp.) (Found: C, 54·8; H, 3·6. $C_{20}H_{17}O_7N_5$ requires C, 54·7; H, 3·9%). The hydrochloride could not be obtained crystalline.

(*b*) A mixture of diphenylacetonitrile (2·5 g.) and dried ammonium thiocyanate (4·0 g.) was heated for 5 hours at 180°. After cooling, the product was treated with hot water (10 c.c.), and the solution filtered. The filtrate was made alkaline with 5N-sodium hydroxide (10 c.c.) and extracted with chloroform. After evaporation of the solvent the residue gave a picrate (0·4 g.), m. p. 224—225°, identical with the above product.

2-*Benzhydryl*-4 : 5-*dihydroglyoxaline* (X).—A mixture of diphenylacetonitrile (9·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.) was heated for 3 hours at 200—210°, during which ammonia was evolved. The cooled mass was extracted with hot water (500 ml.), the mixture made alkaline with 5N-sodium hydroxide (50 c.c.) and extracted with chloroform (200 c.c.). After drying of the solution the chloroform was evaporated off. The residue (61%) is the base, which after recrystallisation from acetone melts at 133—135° (Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 3195, gives 137°). From the base were prepared the picrate, crystallising from ethyl alcohol and melting at 184·5° (Aspinall, *loc. cit.*, gives 185°) (Found: C, 56·6; H, 4·4; N, 15·6. Calc. for $C_{22}H_{19}O_7N_5$: C, 56·8; H, 4·1; N, 15·1%), and hydrochloride, crystallising from ethyl alcohol–ether and melting at 180—182° (Ciba, Austrian P. 150,307; *Zentr.*, 1937, II, 3039, gives 192—193°) (Found: N, 10·0; Cl, 12·5. Calc. for $C_{16}H_{17}N_2Cl$: N, 10·3; Cl, 13·0%).

The authors are indebted to Mr. J. Křeček and Mrs. J. Křečková for testing the above compounds for antihistaminic activity.

RESEARCH AND CONTROL INSTITUTE OF SPOFA,
UNITED PHARMACEUTICAL WORKS,
PRAHA XI, HUSINECKA 11.

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43. *The Determination of the Liquid Density of Chlorine Trifluoride.*

By A. A. Banks and A. J. Rudge.

The liquid density of chlorine trifluoride under its own vapour pressure has been determined over the range −5° to +46° in sealed Pyrex glass dilatometers. Contrary to a previous report, pure chlorine trifluoride was found to have no detectable action on dry Pyrex glass. The results are expressed in the equation $d^t_4 = 1{\cdot}8853 - 2{\cdot}942 \times 10^{-3}t - 3{\cdot}79 \times 10^{-6}t^2$.

The preparation of chlorine trifluoride was first described by Ruff and Krug (*Z. anorg. Chem.*, 1930, **190**, 270), since when only nine communications (Schmitz and Schumacher, *Z. Naturforsch.*, 1947, **2a**, 362, 363; Domange and Neudorffer, *Compt. rend.*, 1948, **226**, 920; Schäfer and Wicke, *Z. Elektrochem.*, 1948, **52**, 205; Booth and Pinkston, *Chem. Reviews*, 1947, **41**, 421; B.I.O.S. Final Report No. 1595; C.I.O.S. Report No. XXII-17) dealing with this compound have appeared in the literature. Ruff and Krug determined some of the physical properties of chlorine trifluoride, but neither they nor any of the later workers have reported a value for the liquid density.

The present determinations were carried out on chlorine trifluoride which was prepared by direct combination of the elements at 280° and purified by passing the vapour over sodium fluoride pellets to remove hydrogen fluoride and then by distillation *in vacuo* to remove more volatile impurities such as chlorine and chlorine monofluoride. In the absence of a precise method of determining fluorine, chemical estimation of the purity of the chlorine trifluoride used was not undertaken.

The dilatometers were calibrated with distilled water after the measurements on chlorine trifluoride had been made; visual examination of the glass at this stage revealed no etching. In calculating the results, all weighings were reduced to vacuum, and the weight of chlorine trifluoride present as vapour was calculated by the equation

$$\log p = 7{\cdot}42 - 1{\cdot}292 \times 10^3/T$$

given by Ruff and Krug (*loc. cit.*). The density values obtained were fitted to a curve of the type $d = a + bt + ct^2$ by the method of least squares, giving the equation

$$d^t_4 = 1{\cdot}8853 - 2{\cdot}942 \times 10^{-3}t - 3{\cdot}79 \times 10^{-6}t^2$$

The experimental results, together with the values calculated from the above equation, are shown in Table I. Table II gives the calculated value of the density of liquid chlorine trifluoride at regular intervals of temperature and at the boiling point. A direct determination of the boiling point has given a value of 12·0° ± 0·1° at 760 mm. of mercury pressure, which is 0·7° higher than that calculated by Ruff and Krug from their vapour-pressure measurements. The determination was carried out in a Pyrex glass apparatus in which pure chlorine trifluoride was refluxed and the condensate allowed to impinge on a thermocouple calibrated against an N.P.L. standard thermometer.

The standard deviation of the calculated values in Table I from the observed values is ±0·0003 g./ml.

Table I.

t.	d (obs.), g./ml.	d (calc.), g./ml.	d (obs.) − d (calc.), 10^{-4}.	$(\Delta d)^2$, 10^{-8}.	t.	d (obs.), g./ml.	d (calc.), g./ml.	d (obs.) − d (calc.), 10^{-4}.	$(\Delta d)^2$, 10^{-8}.
−4·07°	1·8970	1·8972	−2	4	26·90	1·8031	1·8034	−3	9
1·70	1·8806	1·8803	3	9	26·92	1·8036	1·8033	3	9
9·64	1·8566	1·8566	0	0	38·71	1·7654	1·7657	−3	9
12·68	1·8476	1·8474	2	4	38·77	1·7661	1·7655	6	36
20·92	1·8218	1·8221	−3	9	45·63	1·7431	1·7431	0	0
									$\Sigma = 89$

Table II.

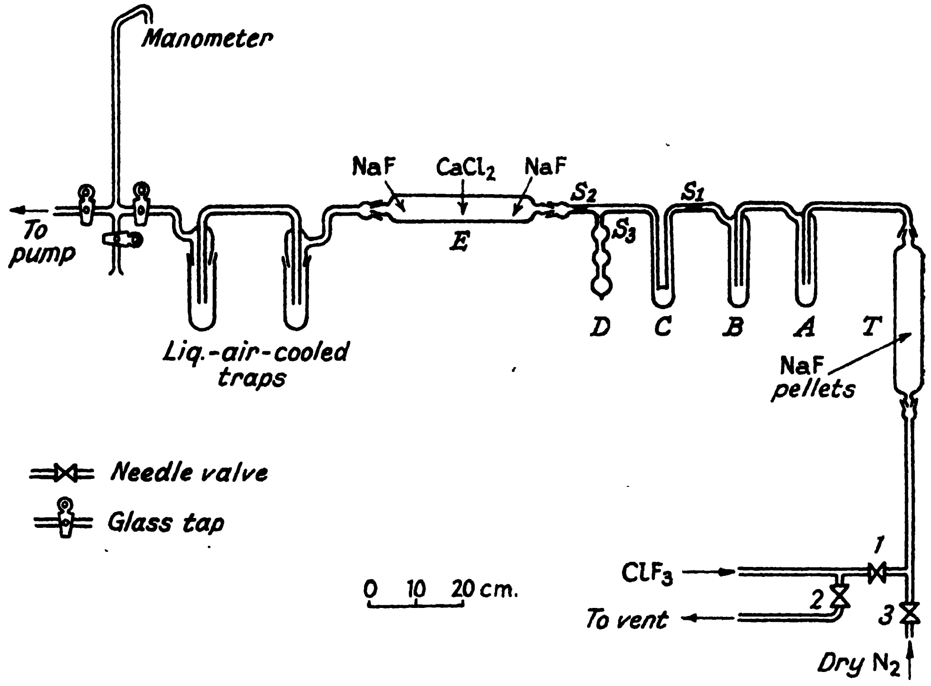
t	0°	10°	12°	15°	20°	25°	30°	35°	40°	45°	50°	60°
d (calc.)	1·8853	1·8555	1·8500	1·8403	1·8249	1·8094	1·7936	1·7777	1·7616	1·7452	1·7287	1·6951

Experimental.

The apparatus used is shown diagramatically in Fig. 1. Except for the three valves (1, 2, and 3), it was constructed entirely of Pyrex glass, the cone joints being sealed with a chloro-fluoro-hydrocarbon wax which had been shown to be inert to chlorine trifluoride vapour at normal temperatures. The valves were Negretti and Zambra needle valves which had been carefully degreased, the gland packings being replaced with asbestos string soaked in a chlorine-trifluoride-resistant chloro-fluoro-hydrocarbon oil. These valves were connected with their seatings towards the apparatus which could therefore be evacuated with the valves closed, without the need for ensuring that the glands were vacuum-tight.

The apparatus was rigorously cleaned and dried before assembly, and all the glassware was baked out *in vacuo* for an hour before use to ensure the complete absence of moisture. Chlorine trifluoride vapour, from a steel cylinder containing the liquid under pressure, was admitted through valve 1, and was diluted with approx. half its volume of dry nitrogen admitted through valve 3. The gas mixture was passed through the hydrogen fluoride absorption tube *T* packed with sodium fluoride pellets, and the chlorine trifluoride was condensed in trap *B* cooled in a solid carbon dioxide–trichloroethylene bath. Trap *A* served to collect any sodium fluoride dust blown from the pellets. When sufficient chlorine trifluoride had been collected in *B*, valves 1 and 3 were closed and the whole apparatus was evacuated. The low-temperature bath was transferred from *B* to *C*, and the chlorine trifluoride was distilled into *C*. During this distillation, any chlorine or chlorine monofluoride, together with a little chlorine trifluoride passed to the calcium chloride tube *E* which served to destroy the fluorides, and chlorine was collected in the traps cooled in liquid air. The trap *C* and dilatometer *D* were sealed off *in vacuo* as a unit at the constrictions S_1 and S_2.

FIG. 1.



The liquid chlorine trifluoride was allowed to warm to room temperature and, by tilting, sufficient chlorine trifluoride was poured into the dilatometer (shown in detail in Fig. 2*A*) to fill it to the required level at the temperature at which measurement was to be made. The dilatometer and trap were then simultaneously cooled in solid carbon dioxide, and the dilatometer was isolated by sealing off at S_2. During cooling of the dilatometer with the trap attached, chlorine trifluoride tended to distil from the dilatometer back to the trap because of the faster cooling of the trap with its smaller volume of liquid. To overcome this, the type of dilatometer shown in Fig. 2*B*, which permits sufficiently accurate adjustment of the quantity of chlorine trifluoride to be made at −78°, was used in the later determinations. By extrapolation of the density results already obtained, the two bulbs were made of such volumes that when the lower bulb was filled with chlorine trifluoride at −78°, the amount of chlorine trifluoride present was sufficient to fill both bulbs at the temperature at which it was intended to carry out the determination.

The thermostat used consisted of a Dewar flask with clear observation strips, filled with dry carbon tetrachloride. This liquid was used in preference to water as a safety precaution, as it had been shown to be stable to chlorine trifluoride up to at least 80°. Temperature control above room temperature was obtained by manual operation of a variable-voltage power pack supplying current at 0—15 volts to a small heating coil immersed in the carbon tetrachloride which was rapidly stirred. A maximum of 3 watts power input was required to maintain the highest temperature used. For temperatures below room temperature, cooling was effected and maintained by the addition of small pieces of solid carbon dioxide. The temperature was measured with a Beckmann thermometer calibrated against a set of N.P.L. standard thermometers. The dilatometer was supported in the thermostat by means of a rigid wire cradle in such a position that the cathetometer measurements were made through a section of the unsilvered strip previously shown to have the minimum optical distortion. The dilatometer was maintained for ½ hour at the temperature (±0·01°) required to bring the chlorine trifluoride meniscus to the centre of one of the lengths of uniform-bore capillary tubing. The height of the meniscus above the lower tip of the dilatometer was measured using the cathetometer, and the temperature was recorded. These measurements were checked after 10 minutes to ensure that temperature equilibrium had been attained. Raising or lowering the temperature enabled a second determination to be made with the other section of uniform capillary tubing.

FIG. 2.

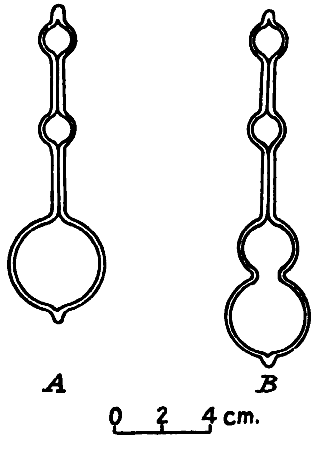
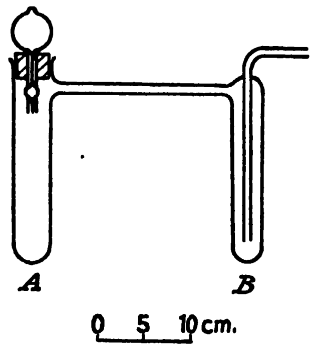


FIG. 3.



The dilatometer was dried, weighed, and then emptied using the apparatus shown in Fig. 3. The dilatometer was inserted into a rubber bung, and a scratch made at the centre of the upper measuring capillary. A sleeve of thin rubber tubing was placed over the scratch and the bulb of the dilatometer was cooled in solid carbon dioxide. The stem was broken under the sleeve, and the fragments of glass, which were retained inside the sleeve, were collected. The dilatometer was immediately inverted in the tube *A* (Fig. 3) which was cooled in solid carbon dioxide and, by means of a water-pump attached to trap *B*, the apparatus was evacuated. The bulk of the chlorine trifluoride was collected in *A*, and the remainder was condensed in trap *B* cooled in liquid air. The dilatometer was removed, rapidly rinsed with water, and then dried.

The dilatometer and glass fragments were weighed and the dilatometer was calibrated to the cut with distilled water at the temperature of the determination. The height of the cut above the tip of the dilatometer was measured with the dilatometer immersed in the thermostat, to minimise any errors due to distortion effects of the Dewar flask walls, and the bore of the capillary was measured by means of a thread of mercury. The volume of liquid chlorine trifluoride at the temperature of the determination could then be calculated. The volume of chlorine trifluoride at the lower temperature of determination was obtained in a similar manner. By a similar technique, the volume of chlorine trifluoride vapour over the liquid was determined and the weight of this vapour calculated as indicated previously.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RUNCORN LABORATORY, CHESHIRE.

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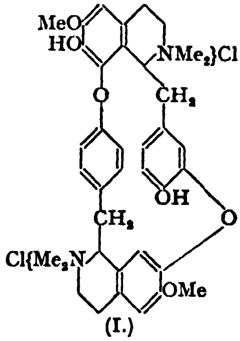
44. *Some New Curarising Agents.*

By JAMES WALKER.

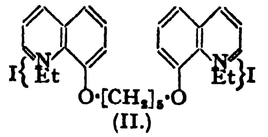
As all of the more potent of the newer curarising agents contain at least two quaternary ammonium groups separated by a chain of about ten atoms, *decamethylene*-1 : 10-*bisdimethylsulphonium di-iodide* (VI) and *decamethylene*-1-*dimethylsulphonium*-10-*trimethylammonium di-iodide* (VIII) have been prepared and examined. Both were found to be powerful curarising agents but to be less active than decamethylene-1 : 10-bistrimethylammonium di-iodide (IV). Succinoylcholine dibromide has also been studied.

ALTHOUGH the curariform activity of 'onium cations has been known for many years, none has, until recently, been known to exert an effect comparable in magnitude with that of the active constituents of native curare. The elucidation of the structure of (+)-tubocurarine chloride (I) by King (*J.*, 1935, 1381; 1939, 1157; 1948, 265) and its introduction as an adjuvant in anæsthesia (Griffith and Johnson, *Anesthesiology*, 1942, **3**, 418; Cullen, *Surgery*, 1943, **14**, 261) have, however, provided a stimulus to further search for other compounds with similar properties.

This work has been recently reviewed by Bovet and Bovet-Nitti (*Experientia*, **1948**, **4**, 325; *Rend. Ist. Superiore di Sanita*, **1949**, **12**, Parte I—III, *Numero speciale sui curari di sintesi*) and by Paton (*J. Pharm. Pharmacol.*, **1949**, **1**, 273), and, as the earlier work relating curariform activity with chemical constitution has been reviewed by Ing (*Physiol. Rev.*, **1936**, **16**, 527) and by Craig (*Chem. Reviews*, **1948**, **42**, 285), it is only necessary to indicate here the trends which recent work has taken. Bisbenzyl*iso*quinoline quaternary salts closely related to, and structurally reminiscent of, (+)-tubocurarine chloride (I) have been shown to have paralysant properties similar to those of (I) (Marsh *et al.*, *J. Pharmacol.*, **1948**, **92**, 454; **1948**, **93**, 109; **1949**, **95**, 100; *Feder. Proc.*, **1949**, **8**, 318; Collier *et al.*, *Nature*, **1948**, **161**, 817; Stoelting *et al.*, *Anesthesia and Analgesia*, **1949**, **28**, 130) but to possess no marked advantages over the latter. Bovet and his collaborators (*Compt. rend.*, **1946**, **223**, 597) attempted to analyse the structure of (+)-tubocurarine chloride (I) and observed marked activity in 1 : 5-bis-(8-quinolyloxy)-pentane diethiodide (3381 R.P.) (II). In subsequent phases of this work, Bovet's group has examined substituted ethers, including choline ethers, of phenols and polyhydric phenols (*ibid.*, **1947**, **225**, 74), among which pyrogallol trisdiethylaminoethyl ether triethiodide (" Flaxedil "), (3697 R.P.) (III) has received clinical application (Mushin *et al.*, *Lancet*, **1949**, I, 726). Choline esters of dibasic aromatic acids were moderately active but their action was more transient (Bovet *et al.*, *Helv. physiol. Acta*, **1948**, **6**, C52).



(I.)



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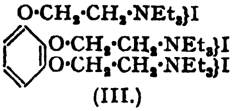
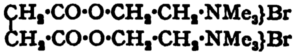
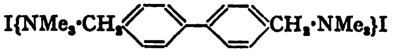
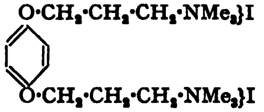

O·CH$_2$·CH$_2$·NEt$_3$}I
O·CH$_2$·CH$_2$·NEt$_3$}I
O·CH$_2$·CH$_2$·NEt$_3$}I

(III.)

The most potent synthetic compound hitherto obtained was discovered independently by Barlow and Ing (*Nature*, **1948**, **161**, 718; *Brit. J. Pharmacol.*, **1948**, **3**, 298) and, in this Institute, by Paton and Zaimis (*Nature*, **1948**, **161**, 718) in decamethylene-1 : 10-bistrimethylammonium di-iodide (C10, " Decamethonium iodide ") (IV), which has already proved satisfactory in clinical use (Organe, Paton, and Zaimis, *Lancet*, **1949**, I, 21; Organe, *ibid.*, p. 773; Davies and Lewis, *ibid.*, p. 775; Hewer *et al.*, *ibid.*, p. 817; Hobson and Prescott, *ibid.*, p. 819). Furthermore, higher and lower homologues were less active than (IV) and pentamethylene-1 : 5-bistrimethylammonium di-iodide (V) actually antagonises the relaxation produced by (IV) (Paton and Zaimis, *Nature*, **1948**, **162**, 810; Organe, Paton, and Zaimis, *loc. cit.*). The feature common to all the more active compounds, despite certain differences in their pharmacological action, is that two quaternary ammonium groups are separated by a chain of between 8 and 12 atoms, indicating that the essential structural requirement for high activity may be that two such groups should occupy positions optimally separated in the same molecule (Barlow and Ing, *loc. cit.*; cf. also Kimura *et al.*, *J. Pharmacol.*, **1949**, **95**, 149). The present communication describes several extensions of this thesis and includes sulphonium types.

Decamethylene-1 : 10- (VI) and *pentamethylene*-1 : 5-*bisdimethylsulphonium di-iodide* (VII), the sulphonium analogues of (IV) and (V), were obtained by the addition of methyl iodide to 1 : 10-*bismethylthio*-n-*decane* and 1 : 5-*bismethylthio*-n-*pentane* respectively. *Decamethylene*-1-*dimethylsulphonium*-10-*trimethylammonium di-iodide* (VIII), a hybrid of (IV) and (VI), was obtained by converting ethyl ω-bromoundecoate into *ethyl ω-methylthioundecoate* and then methylating the 10-*methylthio*-n-*decylamine hydrochloride* obtained by Curtius degradation As the two quaternary ammonium groups in the succinic ester of choline are separated by a chain of 10 atoms, thereby complying with the above postulate, choline succinate dibromide (IX) was prepared and examined. Shortly afterwards it was learned that Bovet and his collaborators had also examined this ester (*Gazzetta*, **1949**, **79**, 129; *Rend. Ist. Superiore di Sanita*, **1949**, **12**, 106), and the appearance of a note by Phillips (*J. Amer. Chem. Soc.*, **1949**, **71**, 3264) on aliphatic dicarboxylic acid aminoethyl ester alkyl iodides is a further indication of the interest aroused in purely aliphatic compounds by the work of Paton and Zaimis (*locc. cit.*). It should be noted in passing that (IX) may be considered as being derived by linking two molecules of acetylcholine through the acetyl groups by the removal of two hydrogen atoms. Although the distance between the two quaternary ammonium groups in (I) is fixed by stereochemical considerations, the separation of the two charged groups in the aliphatic and mixed aromatic–aliphatic types is not uniquely determined, apart from the fact that the two charged groups will be mutually repulsive. As an example of a rigid structure, 4 : 4′-*bis*(*dimethylaminomethyl*)*diphenyl dimethiodide* (X) was prepared, since, in this substance, the fourteen carbon atoms forming the "backbone" of the molecule are coplanar; the compound, however, was found to be less active than (I), (IV), or (IX). 1 : 4-*Bis*-(3-*dimethylaminopropoxy*)*benzene dimethiodide* (XI), obtained by methylation of the corresponding *diprimary amine hydrochloride*, is a higher homologue of the choline ethers of quinol studied by Bovet and his colleagues (*Compt. rend.*, 1947, **225**, 74). The compounds described in the present communication were kindly tested by Dr. W. D. M. Paton and Dr. E. J. Zaimis using the rabbit "head-drop" technique, and the results are recorded above. It is noteworthy that the decline in activity in passing from (IV) to (VIII) and (VI) closely parallels the observations of Ing and Wright (*Proc. Roy. Soc.*, 1933, *B*, **114**, 48) on the relative activities of the tetramethylammonium and trimethylsulphonium ions.

	Compound.	Rabbit " head-drop " dose (mg./kg.).	Mean relative molecular activities.*
(VI.)	$I\{SMe_2\cdot[CH_2]_{10}\cdot SMe_2\}I$	1·7	6·5
(VII.)	$I\{SMe_2\cdot[CH_2]_5\cdot SMe_2\}I$	>38	—
(VIII)	$I\{SMe_2\cdot[CH_2]_{10}\cdot NMe_3\}I$	0·35	31·6
(IX.)	 $\begin{array}{l}CH_2\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NMe_3\}Br\\ CH_2\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NMe_3\}Br\end{array}$	0·15—0·25	48·3
(X.)		1·53	7·8
(XI.)		0·47	27·0
(IV.)	$I\{NMe_3\cdot[CH_2]_{10}\cdot NMe_3\}I$	0·10—0·12	100
(I.)	(+)-Tubocurarine chloride	0·22—0·23	74·0
(III.)	" Flaxedil "	0·5	38·3

* Expressed as percentage of the activity of (IV).

EXPERIMENTAL.

Decamethylene-1 : 10-*diisothiourea Dihydrobromide*.—A solution of decamethylene dibromide (15 g.) and thiourea (7·6 g.) in alcohol (150 c.c.) was refluxed until a test drop of the solution no longer gave a dark precipitate with ammoniacal silver nitrate, about 5 hours being required. The *dihydrobromide* separated from alcohol in clusters of colourless, rectangular plates, m. p. 160—161° (Found: N, 12·7. $C_{12}H_{26}N_4S_2,2HBr$ requires N, 12·4%). The yield was quantitative.

1 : 10-*Bismethylthio*-n-*decane*.—The foregoing dihydrobromide (20 g.) was dissolved in N-sodium hydroxide solution (180 c.c.) with gentle warming on the water-bath, and the small amount of oil which separated was taken into solution by addition of a further small volume of alkali. The cold, filtered, alkaline solution was shaken with methyl iodide (5·6 c.c., 2 mols.) for 3 hours and the resulting oil was extracted with ether, washed with aqueous sodium hydroxide, dried, and recovered (9·64 g.). Distillation afforded the *bismethylthio*-compound as a colourless, mobile oil (8·3 g.), b. p. 195—196°/16 mm., n_D^{20} 1·4946 (Found: C, 61·3; H, 11·1. $C_{12}H_{26}S_2$ requires C, 61·5; H, 11·1%).

Decamethylene-1 : 10-*bisdimethylsulphonium Di-iodide* (VI).—The preceding bisthioether (7·1 g.) was treated with methyl iodide (4 c.c.) and methyl alcohol (2 c.c.) was added. The mixture gradually became viscous when kept at room temperature and solidified on scratching after 2½ days. The *di-iodide* separated from methyl alcohol–ethyl acetate (1 : 1·5) in small, stout, colourless prisms (12·3 g.), m. p. 119—120° (effervescence) (Found: C, 32·7; H, 6·2. $C_{14}H_{32}S_2I_2$ requires C, 32·4; H, 6·2%).

1 : 5-*Bismethylthio*-n-*pentane*.—A solution of pentamethylene dibromide (11·2 g.) and thiourea (7·6 g.) in alcohol (100 c.c.) was refluxed until all the thiourea had reacted; on removal of the solvent the residue crystallised. The crude bisthiuronium bromide was decomposed with 10% aqueous sodium hydroxide solution (120 c.c.) in the manner described above, and the filtrate was shaken for 3 hours with methyl iodide (6·6 c.c.). The *bismethylthio*-compound was a colourless oil (4·8 g.), b. p. 128°/22 mm., $n_D^{18·5}$ 1·5103 (Found: C, 51·4; H, 10·3. $C_7H_{16}S_2$ requires C, 51·2; H, 9·8%).

Pentamethylene-1 : 5-*bisdimethylsulphonium Di-iodide* (VII).—The preceding bisthioether (3·5 g.), methyl iodide (3 c.c.), and methyl alcohol (3 c.c.) were mixed and kept at 37° for 48 hours, the product crystallising out. The *di-iodide* separated from alcohol in colourless, fern-like masses, m. p. 182—183° (effervescence) (Found: C, 24·3; H, 5·0. $C_9H_{22}S_2I_2$ requires C, 24·1; H, 4·9%).

Ethyl ω-Methylthioundecoate.—ω-Bromoundecoic acid (Ashton and Smith, *J.*, 1934, 1308) is conveniently esterified with only one-fifth of the proportions of alcohol and concentrated sulphuric acid recommended by Walker and Lumsden (*J.*, 1901, **79**, 1196). ω-Carbethoxyundecyl*iso*thiourea hydrobromide (26·1 g.), prepared from equimolecular amounts of ethyl ω-bromoundecoate and thiourea in the usual manner, was dissolved in alcohol (50 c.c.) and treated with alcoholic sodium ethoxide (from 1·63 g. of sodium and 25 c.c. of alcohol). After 2 hours at room temperature a further equivalent of alcoholic sodium ethoxide was added. The filtered solution was then treated with methyl iodide (4·7 c.c.); heat was evolved, and the mixture was left at room temperature overnight. The alcohol was removed by distillation, and the *ethyl* ester, recovered in ether, washed, dried, and distilled, was a colourless oil (17·8 g.), b. p. 199—200°/18 mm., n_D^{22} 1·4608 (Found: C, 64·8; H, 10·7. $C_{14}H_{28}O_2S$ requires C, 64·6; H, 10·8%).

Free ω-methylthioundecoic acid, obtained by alkaline hydrolysis of the ester, was a waxy solid and could not be recrystallised easily. The *benzamidine* salt separated from 25% alcohol in colourless, microscopic plates, m. p. 191—192° (Found: C, 65·1; H, 9·0; N, 7·9. $C_{12}H_{24}O_2S,C_7H_8N_2$ requires C, 64·8; H, 9·1; N, 8·0%).

The *hydrazide*, obtained by refluxing the ester with a slight excess of 90% hydrazine hydrate in *n*-propyl alcohol for 5 hours, separated from that solvent in fine, colourless needles, m. p. 88—89° (Found: C, 58·9; H, 10·4; N, 11·7. $C_{12}H_{26}ON_2S$ requires C, 58·5; H, 10·6; N, 11·4%).

10-*Methylthio*-n-*decylamine Hydrochloride.*—The preceding hydrazide (10·5 g., crude) in alcohol (200 c.c.) was treated in a freezing mixture with a concentrated aqueous solution of sodium nitrite (2·6 g.), and concentrated hydrochloric acid (6 c.c.) was added dropwise during about 40 minutes. The mixture was then diluted with ice-water (800 c.c.) and extracted with benzene. The washed benzene extract was dried and warmed slowly on the water-bath and finally boiled for 15 minutes. Most of the benzene was then distilled off and the residue was treated with concentrated hydrochloric acid (25 c.c.) and warmed on the water-bath for a short time. The acid solution was diluted with water, extracted with ether, made strongly alkaline with sodium hydroxide, and again extracted with ether. The resulting oily base (4·9 g.) was treated with excess of alcoholic hydrogen chloride and the alcohol was distilled off. The *hydrochloride* separated from ethyl acetate, or from a small volume of water, in rosettes of small, colourless plates, m. p. 160—161° (Found: C, 55·1; H, 10·8; N, 5·9. $C_{11}H_{25}NS,HCl$ requires C, 55·1; H, 10·9; N, 5·8%).

Decamethylene-1-*dimethylsulphonium*-10-*trimethylammonium Di-iodide* (VIII).—A solution of the preceding hydrochloride (1·2 g.) and sodium hydroxide (1·32 g.) in methyl alcohol (20 c.c.) was refluxed with methyl iodide (3 c.c.) for 7 hours. The neutral solution was filtered from sodium chloride and exhaustively evaporated to dryness with absolute alcohol. The residue was treated with warm acetone to dissolve the sodium iodide and the insoluble product (2·53 g.) was collected and washed with cold acetone. The *di-iodide* separated from absolute alcohol in clusters of colourless plates, m. p. 136—137° (effervescence) (Found: C, 34·7; H, 7·0; N, 2·6. $C_{15}H_{35}NSI_2$ requires C, 34·9; H, 6·9; N, 2·7%).

Di-2-bromoethyl Succinate.—A mixture of ethylene bromohydrin (35·2 c.c.), succinic acid (23·6 g.), benzene (80 c.c.), and concentrated sulphuric acid (1 c.c.) was refluxed for 12 hours on the water-bath. The mixture was diluted with ether and water, and the upper layer was thoroughly washed with sodium hydrogen carbonate solution, dried, and fractionated. The compound was obtained as a pale yellow oil (37 g.), b. p. 169°/3 mm., n_D^{20} 1·5023, crystallising on immersion in a freezing mixture (Found: C, 28·9; H, 3·9. Calc. for $C_8H_{12}O_4Br_2$: C, 28·9; H, 3·6%). Glick (*J. Biol. Chem.*, 1941, **137**, 357) records b. p. 216—217°/26 mm., and Fusco *et al.* (*Gazzetta*, 1949, **79**, 139) record b. p. 150°/1—2 mm.

Succinoylcholine Dibromide (IX).—A mixture of the above ester (25 g.), benzene (18 c.c.), and trimethylamine (9 g.) was heated in a sealed tube at 90° for 8 hours. After cooling, the upper layer of benzene was decanted and the residual gum was triturated with alcohol. The resulting white powder (17·3 g.) was collected, washed with alcohol and dried. The substance separated from absolute alcohol as a colourless, microcrystalline powder, m. p. 211° (Found: C, 37·1; H, 6·4; N, 6·4. Calc. for $C_{14}H_{30}O_4N_2Br_2$: C, 37·4; H, 6·7; N, 6·2%). Fusco *et al.* (*loc. cit.*) record m. p. 219° but no analytical data for this salt, and Glick (*loc. cit.*) records a bromine determination but no m. p.

4 : 4′-*Bis*(*aminomethyl*)*diphenyl Dihydrochloride.*—4 : 4′-Dicyanodiphenyl (23·5 g.) was reduced in methyl-alcoholic ammonia (630 c.c.; 12%) in the presence of Raney nickel (5 g.) with hydrogen at 60 atm. The mixture was warmed to about 65° and reduction was complete in about 2 hours. The catalyst was filtered off, and the solvent removed by distillation, leaving a brown syrup. The crude base was dissolved in excess of 2N-hydrochloric acid, and the solution, treated with charcoal, was concentrated to saturation at the b. p. On cooling, the dihydrochloride crystallised in colourless thin, transparent, rectangular plates (21·3 g.), m. p. above 350° (Found: C, 59·2; H, 6·5; N, 9·9. Calc. for $C_{14}H_{16}N_2,2HCl$: C, 59·0; H, 6·3; N, 9·8%). The observation by Albert *et al.* (*J.*, 1947, 1454) that the crystals of this salt acquire a blue tint on exposure to light was confirmed.

4 : 4′-*Bis*(*dimethylaminomethyl*)*diphenyl Dimethiodide* (X).—The preceding dihydrochloride (2·85 g.) was treated with sodium hydroxide (3·6 g.) and methyl iodide (7 c.c.) in methyl alcohol (60 c.c.) under reflux for 6 hours. The alcohol was distilled off and the residue was crystallised from water, the *dimethiodide* separating in fine colourless needles (4·8 g.), m. p. above 350° (Found: C, 43·4; H, 5·6; N, 4·8. $C_{20}H_{30}N_2I_2$ requires C, 43·5; H, 5·4; N, 5·1%). The crystals of this salt also acquired a blue tint on exposure to light.

1 : 4-*Di*-(3-*aminopropoxy*)*benzene Dihydrochloride.*—1 : 4-Di-(2-cyanoethoxy)benzene (22 g.) (Cook and Reed, *J.*, 1945, 920) was reduced in alcoholic ammonia (500 c.c.; 10%) in the presence of Raney nickel (7 g.) with hydrogen at 20 atm. The catalyst was removed, and the solvent and ammonia were distilled off. The residue was taken up in excess of 2N-hydrochloric acid (charcoal) and the solution was concentrated, affording a crystalline solid (21·1 g.). The *dihydrochloride* separated from 70% alcohol in clusters of colourless, irregular plates, m. p. 313—314° (Found: C, 48·6; H, 7·5; N, 9·2. $C_{12}H_{20}O_2N_2,2HCl$ requires C, 48·5; H, 7·4; N, 9·4%).

1 : 4-*Bis*-(3-*dimethylaminopropoxy*)*benzene Dimethiodide* (XI).—A solution of the preceding dihydrochloride (3 g.) and sodium hydroxide (3·6 g.) in methyl alcohol (50 c.c.) was refluxed with methyl iodide

(6·2 c.c.) for 6 hours. The solid (6·8 g.) which separated from the reaction mixture consisted of the product mixed with sodium chloride. Recrystallisation from alcohol afforded the pure *dimethiodide* in the form of sheaves of colourless needles (5·3 g.), which effloresced on drying, m. p. 267° (Found: C, 36·8; H, 6·5; loss at 100°/vac., 4·5, 4·8. Found, on material dried at 100°/vac.: C, 38·1; H, 6·3; N, 4·8. $C_{18}H_{34}O_2N_2I_2,1\frac{1}{2}H_2O$ requires C, 36·5; H, 6·3; H_2O, 4·6%. $C_{18}H_{34}O_2N_2I_2$ requires C, 38·3; H, 6·0; N, 5·0%).

The author is indebted to Drs. W. D. M. Paton and E. J. Zaimis for undertaking the biological tests, and to Mr. W. A. L. Marshment for assistance in the preparation of starting materials.

**NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
LONDON, N.W.3.**

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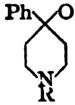
45. *The Synthesis of Piperidine Derivatives. Part IV.* *4-Phenylpiperidols.*

By G. M. BADGER, J. W. COOK, and G. M. S. DONALD.

Attempts to prepare 4-acyloxy-4-phenyl-2 : 2 : 6-trimethyl-1-alkylpiperidines (II) are described. Phenylmagnesium bromide reacted with 2 : 2 : 6-trimethyl-4-piperidone to give 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine*, which readily gave the *N*-methyl derivative. Both compounds were dehydrated to the tetrahydropyridines with great facility, a circumstance which has frustrated the preparation of *O*-acyl and *O*-alkyl derivatives.

THE introduction by Eisleb and Schaumann (*Deut. med. Wochenschr.*, 1939, **65**, 967) of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (" Pethidine ") as an analgesic of considerable potency has stimulated the examination of many new piperidine derivatives. The objective of such work is to prepare not only compounds of greater potency, but also those having no tendency to produce tolerance, drug addiction, and other undesirable side-effects which are characteristic of morphine and some of its derivatives. Although several highly active synthetic analgesics have been obtained it is evident, as a result of the wide clinical use of two of them (" Pethidine," " Amidone ") that the problem of drug addiction has not been solved (see Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 349).

An interesting series of compounds (type I) has been described by Jensen and Lundquist (*Dansk. Tidsskr. Farm.*, 1943, **17**, 173) and by Ziering, Berger, Heineman, and Lee (*J. Org. Chem.*, 1947, **12**, 894). They were obtained by the action of arylmagnesium halides on 1-alkyl-4-piperidones to give carbinols which were esterified with a variety of acids. One of these (I; R = Me, R′ = Et) was shown to have three times the analgesic activity of morphine in the experimental animal. The importance of configuration of the molecule was shown by examination of a further series of compounds similarly obtained from 1 : 3-dimethyl-4-piperidone (Ziering and Lee, *ibid.*, p. 911). The present communication is concerned with attempts to prepare related compounds (of type II) which are related to the natural antispasmodic atropine (III) in the same sort of way that the eucaines are related to cocaine.



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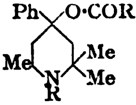

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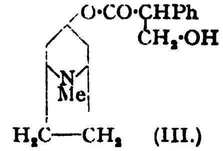

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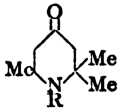

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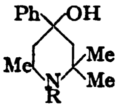

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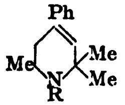

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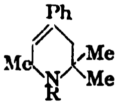

(VII.)

2 : 2 : 6-Trimethyl-4-piperidone (vinyldiacetonamine) (IV; R = H) is readily obtained by condensation of diacetonamine (4-amino-4-methylpentan-2-one) and acetal. (B.P. 101,738), and on treatment with phenylmagnesium bromide gave the desired 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* (V; R = H). This compound is dimorphic, and has m. p.s 91° and 96°. It was characterised as the *hydrochloride, hydrogen oxalate, picrate,* and *acetate.*

1 : 2 : 2 : 6-Tetramethyl-4-piperidone (*N*-methylvinyldiacetonamine) (IV; R = Me) is not

readily available, however, as it cannot be obtained by direct methylation of (IV; R = H) On the other hand, the carbinol corresponding to (IV), namely, 4-hydroxy-2 : 2 : 6-trimethylpiperidine, is easily *N*-methylated directly. As expected, therefore, *N*-methylation of the hydroxy-phenyltrimethylpiperidine (V; R = H) proceeded without difficulty, to give 4-*hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine* (V; R = Me), characterised as the *hydrochloride* and *picrate*.

Both carbinols (V; R = H and Me) were readily dehydrated by warming them with alcoholic hydrogen chloride, to give 4-*phenyl*-2 : 2 : 6-*trimethyl*- (VI or VII; R = H) and 4-*phenyl*-1 : 2 : 2 : 6-*tetramethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine hydrochloride* (VI or VII; R = Me). Indeed, the dehydration was effected with such facility as to render the preparation of *O*-acyl and *O*-alkyl derivatives difficult or impossible, and for this reason attempts to obtain esters of type (II; R = Me) had to be abandoned.

When the magnesium complex from 2 : 2 : 6-trimethyl-4-piperidone and phenylmagnesium bromide was treated with acetic anhydride, the product consisted of a mixture of hydroxyphenyltrimethylpiperidine (V; R = H), phenyltrimethyltetrahydropyridine (VI or VII; R = H), and, curiously, 4-*acetoxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine acetate* (acetate of II; R = H, R′ = Me), which was also characterised as the *hydrochloride*. The formation of this acetate is interesting, as it is evidently formed during distillation, by partial decomposition of acetoxyphenyltrimethylpiperidine with liberation of free acetic acid which then combines with another molecule of acetoxyphenyltrimethylpiperidine, to give the salt. Direct acetylation of hydroxyphenyltrimethylpiperidine (V; R = H), with acetic anhydride, gave 4-*hydroxy*-1-*acetyl*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine*, together with unsaturated material (VI or VII). In the *N*-methyl series, the dehydration was found to be equally ready: under mild conditions, no reaction occurred, while under more vigorous conditions the base underwent almost complete dehydration. This resistance to acetylation is curious, as earlier workers experienced little difficulty in the preparation of compounds of type (I).

EXPERIMENTAL.

4-*Hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* (V; R = H).—To a Grignard solution (50% excess) prepared from bromobenzene (66·8 g.), magnesium (10·2 g.), and anhydrous ether (150 c.c.), 2 : 2 : 6-trimethyl-4-piperidone (20 g.; B.P. 101,738) in ether (25 c.c.) was added dropwise, with stirring. When the vigorous reaction had subsided, the solution was refluxed for a further hour, cooled, and then decomposed with ice and ammonium chloride. After being kept overnight the solid was collected, dried, extracted with ether to remove ether-soluble products, and recrystallised from ethanol–ether. Basification with sodium hydroxide, and extraction with ether, gave 4-*hydroxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* (13 g.) as colourless needles, m. p. 91—92°, from light petroleum (Found: C, 76·7; H, 9·9; N, 6·6. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6; N, 6·4%). After distillation in a vacuum, it was obtained in the form of colourless prisms, m. p. 96—97°, which on repeated recrystallisation from light petroleum, reverted to the needle form, m. p. 91—92°. The *picrate*, prepared in ether and recrystallised from water, formed yellow prisms, m. p. 188—189° (decomp.) (Found: C, 53·6; H, 5·4; N, 12·8. $C_{20}H_{24}O_8N_4$ requires C, 53·6; H, 5·4; N, 12·5%). The *hydrogen oxalate*, prepared in ether and recrystallised from ethanol–ether, formed small colourless needles, m. p. 201—202° (decomp.) (Found: C, 62·2; H, 7·5; N, 4·8. $C_{16}H_{23}O_5N$ requires C, 62·1; H, 7·4; N, 4·5%). The *hydrochloride*, prepared in ether, and crystallised from ethanol–ether, formed colourless prisms, m. p. 247—248° (decomp.) (Found: C, 65·8; H, 8·5; N, 5·7. $C_{14}H_{22}ONCl$ requires C, 65·7; H, 8·6; N, 5·5%). In the preparation of this derivative a small quantity of the product of dehydration (see below) was also isolated. The *acetate* formed colourless prisms, m. p. 223—224° (decomp.), from acetone (Found: C, 69·2; H, 8·9; N, 5·2. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·0%).

4-*Phenyl*-2 : 2 : 6-*trimethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine* (VI or VII; R = H).—A solution of the above hydroxyphenyltrimethylpiperidine (1·75 g.) in ethanol (15 c.c.) was saturated with hydrogen chloride and then heated to 80°, for 6 hours, during which the solution was periodically re-saturated with hydrogen chloride. The solution was then cooled, basified with dilute sodium hydroxide solution, and extracted with ether. Evaporation gave a brown oil, b. p. 90—95°/0·5 mm. (1·5 g.); the pale yellow distillate darkened on storage. 4-*Phenyl*-2 : 2 : 6-*trimethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine hydrochloride*, prepared from the base in ethereal solution, formed colourless prisms, m. p. 266—267° (decomp.), from ethanol–ether (Found: C, 70·6; H, 8·3; N, 6·1. $C_{14}H_{20}NCl$ requires C, 70·8; H, 8·4; N, 5·9%). The *hydrogen oxalate* recrystallised from ethanol–ether in small colourless needles, m. p. 207—208° (decomp.) (Found: C, 65·8; H, 6·9; N, 5·1. $C_{16}H_{21}O_4N$ requires C, 66·0: H, 7·2; N, 4·8%).

4-*Acetoxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine*.—2 : 2 : 6-Trimethyl-4-piperidone (5 g.) was treated with a 50% excess of phenylmagnesium bromide, as above, and the solution heated under reflux for 13 hours. Acetic anhydride (11 g.), in ether, was added to the cooled solution, which was then refluxed for a further 9 hours, cooled, and hydrolysed with ice and 6N-hydrochloric acid. The aqueous layer was separated, basified, and extracted with chloroform. Distillation of the residue gave 2 : 2 : 6-trimethyl-4-piperidone (0·7 g.) and a yellow oil (0·3 g.), b. p. 110—130°/2 mm. When the oil was set aside, a small amount of crystals separated and on recrystallisation from ethanol–ether gave 4-*acetoxy*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine acetate* as colourless prisms, m. p. 176—177° (Found: C, 67·1; H, 8·1; N, 4·6. $C_{18}H_{27}O_4N$

requires C, 67·3; H, 8·4; N, 4·4%). 4-*Acetoxy-4-phenyl*-2 : 2 : 6-*trimethylpiperidine hydrochloride*, obtained in the usual way from the above acetate, formed colourless prisms, m. p. 238—239° (decomp.), from ethanol–ether (Found: C, 64·3; H, 7·9; N, 4·8. $C_{16}H_{24}O_2NCl$ requires C, 64·5; H, 8·1; N, 4·7%). The residual oil from the distillate was dissolved in ether and treated with hydrogen chloride. Crystallisation from ethanol–ether gave colourless prisms, m. p. 264—265° (decomp.), of 4-phenyl-2 : 2 : 6-trimethyl-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-tetrahydropyridine hydrochloride, identified by direct comparison with a specimen prepared as above, and also by analysis (Found: C, 70·9; H, 8·3; N, 5·4%).

Direct acetylation of 4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (1 g.) by refluxing it with acetic anhydride (5 g.) for 5 minutes, followed by basification and extraction with chloroform, gave a colourless solid. After being washed with dilute hydrochloric acid to remove basic material, and recrystallised from light petroleum, 4-*hydroxy*-1-*acetyl*-4-*phenyl*-2 : 2 : 6-*trimethylpiperidine* was obtained as colourless needles, m. p. 112—113° (Found: C, 73·2; H, 8·8; N, 5·1. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

4-*Hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine* (V; R = Me).—A mixture of 4-hydroxy-4-phenyl-2 : 2 : 6-trimethylpiperidine (2 g.), and 40% aqueous formaldehyde (2 g.) was heated to 100°. After an hour, a vigorous reaction occurred, and the whole mass solidified. The solid was washed free from formaldehyde with water and recrystallised from light petroleum. 4-*Hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine* (2 g.) formed colourless needles, m. p. 133—134° (Found: C, 77·4; H, 9·7; N, 6·2. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9; N, 6·0%). The *hydrochloride*, prepared in ether and recrystallised from ethanol–ether, formed colourless prisms, m. p. 243—244° (decomp.) (Found: C, 66·8; H, 8·9; N, 5·4. $C_{15}H_{24}ONCl$ requires C, 66·8; H, 8·9; N, 5·2%).

Attempted Acetylation of 4-*Hydroxy*-4-*phenyl*-1 : 2 : 2 : 6-*tetramethylpiperidine*.—The esterification of carbinols of similar structure was reported by Jensen and Lundquist (*loc. cit.*), and by Ziering *et al.* (*loc. cit.* and *J. Org. Chem.*, 1947, **12**, 904). Their methods have been used and extended in attempts to acetylate 4-hydroxy-4-phenyl-1 : 2 : 2 : 6-tetramethylpiperidine, but without avail. Thus, treatment with acetyl chloride in the cold, with or without an inert solvent (ether, benzene) resulted in complete dehydration to (VI or VII; R = Me) within 48 hours. Acetic anhydride under similar conditions did not react, and heating at 100° or boiling under reflux with acetic anhydride and sodium acetate, pyridine, or a trace of concentrated sulphuric acid caused dehydration in varying degrees.

An unsuccessful attempt was also made to achieve acetylation by treatment with ethylmagnesium bromide, followed by reaction of the resulting magnesium complex with cold acetic anhydride (Houben, *Ber.*, 1906, **39**, 1736).

4-*Phenyl*-1 : 2 : 2 : 6-*tetramethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine* (VI or VII; R = Me).—A solution of the above hydroxyphenyltetramethylpiperidine (0·5 g.) in ethanol (10 c.c.) was saturated with hydrogen chloride and heated to 80° for 7 hours, during which the solution was periodically re-saturated with hydrogen chloride. Basification with sodium hydroxide, and extraction with ether, gave a brown oil. 4-*Phenyl*-1 : 2 : 2 : 6-*tetramethyl*-1 : 2 : 5 : 6(or 1 : 2 : 3 : 6)-*tetrahydropyridine picrate* was prepared from this oil in ethanol and, after recrystallisation from ethanol formed yellow needles, m. p. 161—162° (decomp.) (Found: C, 57·5; H, 5·4; N, 12·6. $C_{21}H_{24}O_7N_4$ requires C, 57·6; H, 5·4; N, 12·6%).

One of us (G. M. B.) has held an I.C.I. Research Fellowship during this work, and we also thank the Department of Scientific and Industrial Research for a Maintenance Allowance (to G. M. S. D.). Microanalyses have been carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW.

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46. *The Automatic Recording of Freezing-point Curves.*

By E. F. G. HERINGTON and R. HANDLEY.

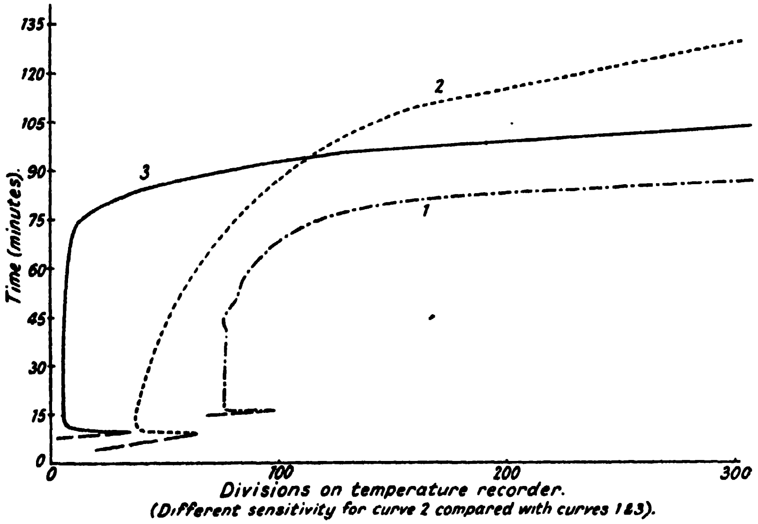
The methods in general use for securing adequate mixing of the solid and liquid during the determination of purity by the freezing-point method are reviewed, and modifications of technique are described which avoid some of the difficulties inherent in the current procedures.

RECORDS of the variation of temperature with time obtained during the freezing of a liquid are now widely used as the basis of a test for chemical purity. The conditions under which such curves can be employed to determine the impurity in a given sample have been discussed by a number of investigators (White, *J. Physical Chem.*, 1920, **24**, 393; Mair, Glasgow, and Rossini, *J. Res. Nat. Bur. Stand.*, 1941, **26**, 591; Taylor and Rossini, *ibid.*, 1944, **32**, 1947; Glasgow, Streiff, and Rossini, *ibid.*, 1945, **35**, 355; Stull, *Ind. Eng. Chem.*, *Anal.*, 1946, **18**, 234; Schwab and Wichers, "Temperature, its measurement and control in science and industry," p. 256; Glasgow, Beadle, Axilrod, and Rossini, *Ind. Eng. Chem.*; *Anal.*, 1948, **20**, 460).

Essential conditions for the application of the freezing-point method are the maintenance of thermodynamic equilibrium between the liquid and crystallised solid while heat is withdrawn from the system at a controlled rate. These conditions are usually maintained by stirring vigorously and by using a cooling bath some 80° lower in temperature than the freezing point of the sample under investigation. The rate of cooling is selected by varying the gas pressure in the jacket surrounding the specimen during the preliminary cooling. The temperature of the solid–liquid system can be measured by means of a platinum resistance thermometer and the time–temperature curve can be obtained manually but this method is so laborious that Stull (*loc. cit.*) has developed an automatic temperature recorder which is activated by a small platinum resistance thermometer. We have recently described an apparatus for recording temperature changes which makes use of a thermistor as the temperature-sensitive element (Herington and Handley, *J. Sci. Inst.*, **1948**, **25**, 434). For any desired temperature sensitivity a more robust recorder can be used with a thermistor than is required by a platinum resistance thermometer, and moreover the heat capacity of a thermistor is very small. The advantages of using small thermometers of low heat capacity in the freezing-curve technique were recognised early in the history of the subject by White (*loc. cit.*).

Various types of motor-driven stirrers which may be used in the freezing-point apparatus have been described by Rossini *et al.* (*loc. cit.*) but these all cease to operate when only a fraction of the liquid has frozen. This failure of the stirrer affects the rate of cooling and as a result a change of direction in the curve suddenly appears at the point where the stirrer stops (see Fig. 1, curve 1). Inspection of curves obtained by other observers reveals that this behaviour is common and is not peculiar to the mechanically-stirred equipment which we used at the outset of our work. In motor-stirred apparatus the liquid is usually protected from contact with atmospheric moisture by the passage over the liquid surface of a stream of purified air which is allowed to escape through the gland around the shaft of the stirrer.

FIG. 1.



Curve 1.—*Obtained with mechanical stirrer.*
Curves 2 *and* 3.—*Obtained with apparatus described in this paper.*

An alternative method for securing mixing and preventing contact with moist air is to use a sealed-in stirrer operated by a solenoid (Stull, *loc. cit.*), but in this case also the stirrer stops at rather an early stage during the freezing and it is necessary to ensure that no electrical interference is produced in the temperature-measuring circuit by the current in the solenoid.

Schwab and Wichers (*loc. cit.*) have sought to overcome these difficulties by employing a stream of gas bubbles introduced into the liquid through a fine sintered-glass diaphragm. This method has much to recommend it but is not particularly suitable for work when a large number of compounds is to be examined, because of the difficulty of cleaning and drying the sintered-glass plates.

In the apparatus we describe, adequate mixing has been obtained by applying a pulsating gas pressure to the liquid surface in such a way as to produce oscillations in a U-shaped column of the liquid being frozen. Thus mixing of the liquid phase continues until practically all the specimen has frozen while at the same time the material is kept out of contact with moist air. The apparatus is easily cleaned and only 10 c.c. of liquid are required for a determination of the freezing-point curve.

EXPERIMENTAL.

The temperature-recording equipment and the freezing-point apparatus will be discussed separately although they are in fact interdependent units.

Recording of Temperature Changes.—The thermometric equipment used was similar to that described previously as suitable for temperatures from −40° to 140° (Herington and Handley, *loc. cit.*), except that a Tinsley D.C. amplifier and pen recording millivolt-meter have replaced the photographically-recording galvanometer. A constant-voltage transformer smooths the input to the amplifier. The amplifier and recorder have two sensitivity ranges corresponding to 5 and 20 mv. for a full-scale deflection on the chart. A less sensitive galvanometer has been incorporated in the circuit to assist in the preliminary balancing of the bridge and press-button switch-gear has been used so that the out-of-balance current of the bridge can be fed to the recorder or galvanometer at will.

As an indication of the sensitivity which can now be obtained it has been established that a full-scale deflection of 100 divisions (3½ in.) is equal to a difference of 0·24° for temperatures around 5·5° with use of the 5-mv. range on the recorder and a thermistor of approx. 2000 ohms resistance at room temperature when there is an E.M.F. of 4 volts across the bridge.

Thermistors can be used at temperatures as low as −130° and may thus be employed, for example, to study the freezing-point characteristics of samples of *n*-pentane. We are indebted to Messrs. Standard Telephones and Cables Ltd. for a special type F thermistor having a resistance at room temperature of 200 ohms which increases to approx. 2·5 megohms at −130°. A sensitivity of 0·62° per 100-divisions deflection of the recorder pen at −130° has been obtained by using this thermistor as part of one of the variable arms of a bridge of 11 megohms with two ratio arms of 1 megohm each, and with 120 volts from a dry battery applied across the bridge.

Vapour-pressure thermometers constructed according to the design of Stock (*Z. Electrochem.*, 1923, **29**, 354), but with an additional pocket for the thermistor, may be used for the calibration of thermistors at low temperatures. The temperature during the calibration must be allowed to fall slowly in order to avoid difficulties which may arise from the different speeds of response of the two temperature-sensitive elements.

Freezing-point Apparatus.—The dimensions of the apparatus are of some importance and are indicated in Fig. 2 which is drawn to scale. A fluctuating gas pressure is produced in the gas line *F* by means of the pulsing meter *E*. The construction of this meter and its use in another connection have been described in a communication from this laboratory (Preston and Worthington, *Chem. and Ind.*, 1947, p. 612). Compressed air for working the meter has been obtained from a large compressor delivering gas at 20 lbs. per sq. in., but we have established that a satisfactory source is an ordinary small rotating blower of the type commonly used by glass blowers. The air stream causes the pressure to rise in the gas line *F* until the mercury is driven over the narrow loop in *E*, and then the pressure in *F* suddenly drops. These pressure fluctuations set up oscillations of the liquid in the U tube. The gas above the liquid in the left-hand limb of the U tube is alternately compressed and expanded by reason of the pressure pulses, and this produces oscillations in the mercury manometer *M*. The volume of the gas in the compression chamber *L* is fairly critical and can be adjusted when the apparatus is first set up by varying the amount of mercury in *L* until the best mixing of the liquid in the U tube is obtained. The movement of the mercury in *M* gives a visual indication of the rate and magnitude of the surging of the liquid which is being frozen. The main air stream passes to waste after traversing the trap *T*, immersed in liquid air, which has been inserted to reduce the vapour pressure of mercury in the effluent gas. The gas which pulsates to and fro immediately above the liquid in the right-hand limb of the U tube slowly interchanges with the gas in the line *F*. The liquid sample is protected from any impurities in this main air line by the column of silica gel *G*.

Efficient mixing in the U tube is produced by the stainless-steel helices of external diameter 3/8 in., made of wire of 1/16-in. diameter.

The U tube has square corners to allow the thermistor pocket to terminate at a point very near the bottom of the left hand limb. The position of the sensitive thermistor tip is important as visual inspection has shown that the last drops of liquid collect at this point at a time when the whole charge is nearly frozen. The thermistor is inserted in the pocket so that the sensitive tip is 1 mm. from the bottom of the inside of the pocket.

The design of the helices was conditioned by the following observations. Adequate mixing does not occur if the U tube is employed without helices, for the liquid then moves as a whole with merely local turbulence. On the other hand, restriction of free movement by too many baffles causes the liquid to become trapped in small pockets, and then the thermistor fails to record the temperature of the bulk liquid–solid mixture. The result of inadequate mixing is to produce a freezing curve of the wrong shape (see page 203 for a discussion on the shape of the curve).

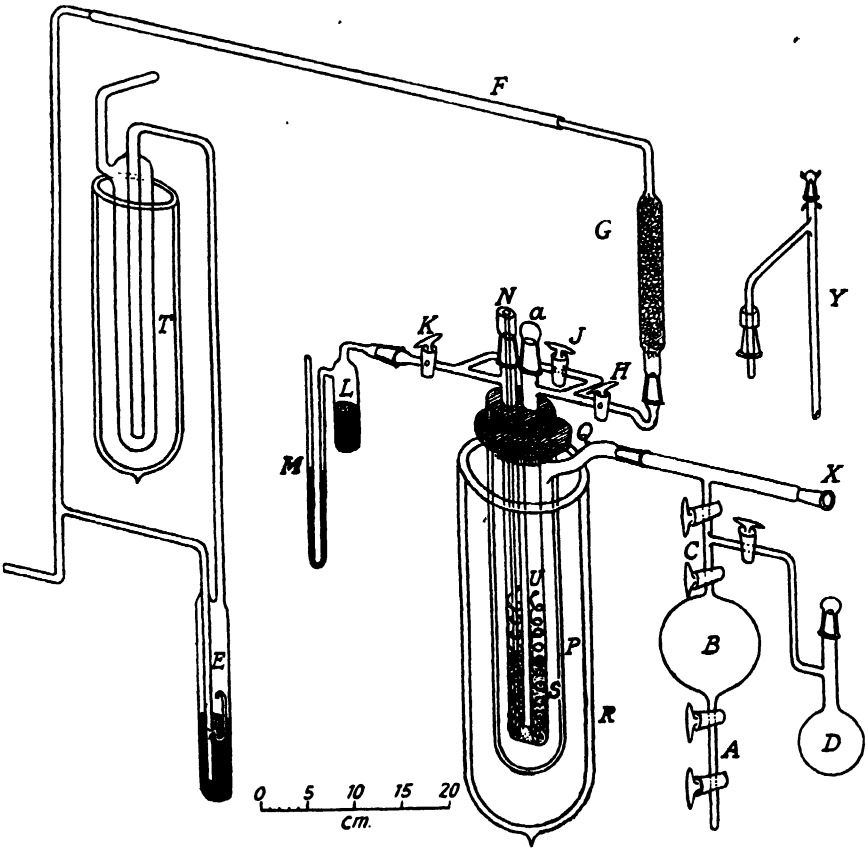
The gas in the left-hand section of the U tube is in a closed system bounded by the mercury in the manometer *M* on one side and by the liquid in the freezing-point apparatus on the other, and therefore as the system cools the pressure of this gas falls. The average gas pressure in the other limb of the U tube however remains constant, because as the temperature falls more air is taken in from the line *F*. The pressures in the two sections can be equalised by manipulating the tap *J*, and this is done from time to time during the preliminary cooling.

Cooling media suitable for different freezing temperatures have been suggested elsewhere (*e.g.*, Glasgow, Streiff, and Rossini, *loc. cit.*). The rate of cooling is adjusted by varying the gas pressure in the Dewar jacket *P* during the preliminary stages of cooling. The jacket is silvered except for two strips 0·5 × 8 cm. which are used as inspection windows. The jacket *P* can be evacuated by means of a mercury-vapour pump backed by a Metrovac oil pump with a trap immersed in liquid nitrogen inserted in the gas line to remove traces of mercury vapour (not shown in Fig. 2). The system of vessels, *A*, *B*, *C*, and *D* (Fig. 2) has proved to be useful for the introduction of controlled amounts of air to the vacuum jacket. The approximate volumes used were *A* = 0·6 c.c., *B* = 500 c.c., *C* = 1·2 c.c., and *D* = 150 c.c. Dry air at atmospheric pressure is admitted into *A*, and portions of this mass of gas can be expanded into *B*, *C*, and *D*, and finally a selected volume of this gas at a low pressure can be admitted to the jacket *P*.

The U tube must be held symmetrically within the jacketted vessel *P*, and centring of the tube is ensured by the wooden platform *Q* which is held rigidly in position by a collar (see Fig. 2).

The method chosen to induce crystallisation in the slightly supercooled liquid depends upon circumstances. A convenient method, when it can be applied, is to employ the apparatus *Y* (Fig. 2) which can be connected to the U tube by interchange with the ground glass joint *a*. Two steel ball bearings, 3/32″ in diameter, are cooled in the vertical tube of *Y* just before seeding is required. These balls can be moved up the tube by means of a permanent magnet and allowed to fall down the sloping tube into the right-hand side of the U tube when crystallisation is to be induced. This method does not always produce successful results with liquids which supercool readily or with liquids which freeze at a very low temperature, but where this technique can be employed contamination of the sample with moisture is avoided. An alternative method is to insert a cooled stainless-steel rod through *a* (Fig. 2) while the pulses are momentarily stopped, but even this simple procedure can yield erratic results with substances having more than one crystalline form (*e.g.*, α-picoline). In such circumstances an injector made by passing a thin stainless-steel rod down the centre of a close-fitting glass tube has proved useful because a plug of solid can be caused to crystallise in the tip of the ejector and can then be held until seeding is required at some temperature at which the desired crystalline form is stable. The solid can be ejected into the supercooled liquid by a thrust on the stainless-steel plunger.

FIG. 2.



A, B, C, D. Gas volumes for doser.
E. Pulsing meter.
F. Gas line.
G. Silica gel.
H, J, K. Taps, 4 mm. bore.
L. Compression chamber.
M. Mercury manometer.
N. Cap carrying thermistor pocket.
P. Dewar flask with variable vacuum.
Q. Wooden platform supporting U *tube.*
R. Dewar flask containing cooling medium.
S. Stainless steel helices.
T. Trap in effluent gas line.
U. U *tube containing liquid under examination* (46 *cm. in length, tube* 11 *mm. I.D.*).
X. Joint to high vacuum line.
a. Glass cap (*B.* 19) *which can be interchanged with seeding arrangement Y.*
Y. Seeding apparatus containing ball bearings.

The only heat liberated by the stirring in the present equipment is that produced by the friction of the liquid against the obstacles used to produce turbulence. Direct measurement on a typical example has shown that at 106 pulses per minute this heat is generated at approx. 7% of the rate at which heat is extracted in the cooling process.

Recording of the Freezing-point Curves.—10 C.c. of liquid samples may be used in the apparatus, although it is preferable to use double this amount. To carry out a determination the apparatus is assembled, the resistances in the arms of the Wheatstone bridge are adjusted to values suitable for the temperature at which freezing will occur, pressure in the two limbs of the U tube is equalised, and the pulses are started at a rate of 106 per minute. The Dewar vessel *R* (Fig. 2) containing the refrigerant is placed in position and, if a very wide temperature interval has to be covered before the freezing temperature is reached, dry air is admitted to the vacuum jacket *P* through a tap on the vacuum line (not shown) in order to accelerate the cooling. The jacket *P* is evacuated as soon as the temperature has fallen sufficiently, and doses of air at low pressure are admitted through the system *A*, *B*, *C*, *D*, until the desired cooling rate has been obtained. Rates are normally selected so that the total time of freezing is approx. 1½ hours. From time to time the levels of the liquid in the U tube are balanced by means of tap *J* (Fig. 2).

Crystallisation is induced by one of the methods described above. The liquid levels are balanced immediately following each attempt at seeding, but are not again adjusted once crystallisation has started. The temperature–time curve is then plotted on the recorder.

TREATMENT OF EXPERIMENTAL OBSERVATIONS.

The theory of the use of freezing-point curves for determining impurities has frequently been discussed (see page 199 for references). The assumption that the main component crystallises first, leaving the impurity in the liquid is common to all these treatments.

White (*loc. cit.*) appears to have been the first to recognise that, if under these conditions the depression of the freezing point is proportional to the mol. fraction of impurity in the liquid, then the temperature difference between the initial freezing point and that when half the material is frozen is equal to the temperature depression originally produced by the impurity. The molar percentage of impurity and the true freezing point of the pure material can thus be found.

Rossini *et al.* (*loc. cit.*) have discussed a thermodynamically more exact approach which involves higher approximations, but for many purposes the simpler treatment appears to be sufficient, particularly since, as Schwab and Wichers (*loc. cit.*) point out, the rate of cooling is rarely, if ever, exactly constant. Schwab and Wichers therefore suggest that the amount of impurity be calculated by proportional parts from a freezing-point curve of the original material and from another curve for the same material obtained after a known amount of impurity has been added. Both curves should be measured under the same conditions.

In view of the uncertainties inherent in the technique we have used the simple method of calculation employed by Stull (*i.e.*, essentially White's method) when the cryoscopic constant has already been reported and when a high accuracy is not required. If a higher accuracy is needed or if the cryoscopic constant is not known, Schwab and Wicher's method of proportional parts is used.

The efficacy of any equipment for determining freezing-point curves can be examined by analysing the shape of the curves. Subject to the usual assumptions it follows from the argument used by White that

$$[(1 - x)/x]\Delta t = t^{\circ} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

where Δt is the difference between the temperature at the initial freezing point at time z_0 and that at time z, x is the fraction frozen at time z, and t° is the depression of the freezing point of the pure component produced by the impurity originally present.

If the cooling rate is constant, then approximately

$$x = (z - z_0)/(z_t - z_0) \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

where z_0 is the time when freezing starts, z_t is the time when all the liquid has frozen, and z is the time when a fraction x is frozen.

The form of these equations shows that, on the temperature–time plot, Δt should increase as z increases, and that the rate of increase of Δt with time should itself increase with z. Fig. 1, curves 2 and 3, shows that smooth curves are obtained with the present apparatus and that they are qualitatively of the correct shape.

If equations (1) and (2) are obeyed, then $[(1 - x)/x]\Delta t$ and $[(z_t - z)/(z - z_0)]\Delta t$ should be constant. The table contains the more detailed analysis of some experimental results obtained with 20-c.c. samples for which x has been calculated from equation (2) and Δt is expressed in arbitrary units equal to the deflection of the galvanometer in divisions. These units have different values in terms of temperature for the two samples.

Values of $[(1 - x)/x]\Delta t$. *Total time of curves* = 86 *mins.*

	$[(1 - x)/x]\Delta t$.			$[(1 - x)/x]\Delta t$.	
x, calc. from equation (2).	Benzene, 99·73 mols.-% pure.	2 : 6-Lutidine, 99·1 mols.-% pure.	x, calc. from equation (2).	Benzene, 99·73 mols.-% pure.	2 : 6-Lutidine, 99·1 mols.-% pure.
0·1	13·5	23	0·6	12·6	28
0·2	10·0	24	0·7	12·4	24
0·3	10·5	28	0·8	12·0	19
0·4	12·0	30	0·9	9·0	11
0·5	13·0	31			

The table indicates that the curves obey equations (1) and (2) up to $x = 0·70$, and therefore equilibrium between solid and liquid would appear to be maintained until 70% of the charge is frozen.

The freezing-point results for 184 hydrocarbons obtained by the reciprocating-stirrer method recorded in the "Supplement to National Bureau of Standards Circular 398" (January 1st, 1949) have been analysed by us to provide a standard of accuracy against which to compare the performance of our apparatus. The results in the Circular are expressed as mol.-% of impurity ± a certain percentage. The parameter most directly measurable by the freezing-point method is the impurity, so that it is natural to express the uncertainty of the results as a fraction of the impurity. The mean value of the ratio ± percentage/mol. percentage for the 184 hydrocarbons listed is 0·54, *i.e.*, the value designated as ± is usually approximately one-half of the impurity determined. Thus a sample would be described as 99·6 ± 0·2 mols.-% pure.

A sample of benzene which was found to be 99·90 mols.-% pure in the present apparatus, with the method of calculation employed by Stull and a cryoscopic constant of 5·12° per 1000 g. of benzene gave a value of 99·77 mols.-% pure by the proportional-parts method. To the same sample of benzene was added in succession 0·048 and 0·144 mol.-% of impurity, *i.e.*, impurity in the ratio 1 : 3, and the depressions of temperature when the samples were half frozen were as 1 : 3·5.

The apparatus described thus appears to yield results at least as accurate as the methods in common use.

Our thanks are due to Mr. A. J. Cook for assistance with the experimental work and to Mr. C. G. Andrews for carrying out the construction of numerous models in glass which were used in the development of the design discussed here. The work described above has been carried out as part of the research programme of the Chemical Research Laboratory and this paper is published by permission of the Director of the Laboratory.

Chemical Research Laboratory,
Teddington, Middlesex.

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47. *The Preparation of the Mononitrobenzaldehydes.*

By W. Davey and J. R. Gwilt.

o- and *p*-Nitrobenzaldehydes have been prepared by the oxidation of the corresponding nitrocinnamic acids. Nitration of benzylidene diacetate in acetic acid or anhydride solution with copper nitrate yields *p*-nitrobenzylidene diacetate, whilst nitration of the diacetate in acetic anhydride solution with nitric acid gives *o*-nitrobenzylidene diacetate. Nitration of acetophenone in acetic acid solution with copper nitrate yields *p*-nitrobenzylidene diacetate, and the mechanism of this reaction has been elucidated. Other metal nitrates are less effective than copper nitrate as nitrating agents for benzylidene diacetate. Hydrolysis of nitrobenzylidene diacetates is satisfactorily achieved by the use of suspensions of magnesium hydroxide.

MONONITROBENZALDEHYDES were required for the preparation of substituted benzaldehydes and of substituted chalcones; *m*-nitrobenzaldehyde is readily prepared by the direct nitration of benzaldehyde but the preparation of the *o*- and *p*-isomers presents some difficulties. Although some *o*-nitrobenzaldehyde is produced in the direct nitration of benzaldehyde (Friedländer, *Ber.*, 1881, **14**, 2803) it cannot easily be isolated from the reaction product. The preparation of *o*- and *p*-nitrobenzaldehydes has been investigated by three methods: (*a*) oxidation of the nitrotoluenes by the chromic acid–acetic acid–anhydride method, (*b*) oxidation of the nitrocinnamic acids, and (*c*) nitration of benzaldehyde and of its diacetate.

Oxidation of nitrotoluenes by the methods of *Org. Synth.*, Coll. Vol. II, p. 441, and Vol. **24**,

p. 75, gave the required products, but from *o*-nitrotoluene large amounts of tar were always obtained and the yield of aldehyde was low. In view of this and of the considerable risk of explosion attendant on the use of chromic acid in acetic anhydride (Tuey, *Chem. and Ind.*, 1948, 766), alternative methods of preparation were investigated.

Acetyl or benzoyl nitrate has been used for selective *ortho*-nitration of organic compounds but their use is limited by the risk of explosion (Pictet and Khotinsky, *Ber.*, 1907, **40**, 1163). Menke (*Rec. Trav. chim.*, 1925, **44**, 141, 269) has shown that acetic anhydride and copper, nickel, iron, or cobalt nitrate effect *ortho*-nitration in the same way as acetyl nitrate, but without the danger of explosion. Bacharach (*J. Amer. Chem. Soc.*, 1927, **49**, 1522) has confirmed this and shown that lithium nitrate yields mainly *p*-nitro-compounds. Nitration of cinnamic acid in acetic anhydride solution by means of hydrated copper nitrate failed to give *o*- and *p*-nitrocinnamic acids, which were therefore prepared by nitration of cinnamic acid or of its ethyl ester in nitric acid alone, or preferably in sulphuric acid, the acids being separated by utilising the low solubility of ethyl *p*-nitrocinnamate in ethanol (Drewson, *Annalen*, 1882, **212**, 150). Nitration of benzylidene diacetate, prepared from benzaldehyde by the method of Wegschneider and Späth (*Monatsh.*, 1909, **30**, 840), in acetic anhydride solution by means of hydrated copper nitrate yielded *p*-nitrobenzylidene diacetate in 52% yield, but the reaction was difficult to control an dnitration was therefore effected (in 79% yield), using acetic acid as solvent. Careful purification of benzaldehyde was essential for maximum yields, even redistilled samples of the aldehyde reacted violently with acetic anhydride with excessive evolution of heat. Attempts to moderate the reaction between impure benzaldehyde and acetic anhydride by the addition of acetic acid were not successful and led to incomplete formation of diacetate. Nitration of benzylidene diacetate, formed *in situ*, from pure benzaldehyde has also been achieved by this method. Commercial samples of benzaldehyde have been nitrated in acetic acid solution with copper nitrate to give *p*-nitrobenzylidene diacetate in 12% yield, although it has not proved possible to prepare benzylidene diacetate from benzaldehyde and acetic acid by a method analogous to that using acetic anhydride (cf. Wegschneider and Späth, *loc. cit.*). Other metal nitrates were found to be less useful than copper nitrate in these reactions, lead nitrate failing to react and sodium nitrate causing deflagration.

Baker and Ingold (*J.*, 1930, 431) showed that the nitration of benzaldehyde with acetic anhydride and nitric acid gave 62·6% of *o*–*p*- and 37·4% of *m*-nitration, the reaction proceeding *via* the diacetate (*p*-nitrobenzylidene diacetate was isolated from the reaction mixture). The change in position of nitration with different experimental conditions has been summarised by Baker and Moffitt (*J.*, 1931, 316). Nitration of benzylidene diacetate, formed *in situ*, in acetic anhydride solution with nitric acid was vigorous and led to *o*-nitrobenzylidene diacetate (43%) and *p*-nitrobenzoic acid (26%), whilst nitration at low temperatures gave *o*-nitrobenzaldehyde in 41% yield. A mixture of nitric and sulphuric acids, at low temperatures, gave *o*- and *m*-nitrobenzaldehyde in 33% and 43% yield, respectively. Excess of sulphuric acid led to the hydrolysis of the diacetate and formation of *m*-nitrobenzaldehyde as the main product. This *ortho*-nitrating effect of nitric acid–acetic anhydride has previously been reported by Witt and Uterman (*Ber.*, 1906, **39**, 3903) and the preparation of *o*-nitrocinnamic aldehyde in 36% yield by Mills and Evans (*J.*, 1920, 1037) is a further example for *o*-nitro-aldehydes. Nitric acid, in contrast to copper nitrate, fails to nitrate benzylidene diacetate in acetic acid solution.

Ketones do not form diacetates, but acetophenone undergoes oxidation and nitration to *p*-nitrobenzylidene diacetate in 40% yield when treated with acetic acid and copper nitrate. The mechanism of this reaction has been found to involve oxidation of the acetophenone to benzoylformic acid, loss of carbon dioxide to give benzaldehyde, formation of benzylidene diacetate, and nitration. Benzoylformic acid yields benzylidene diacetate on heating with acetic anhydride, and *p*-nitrobenzylidene diacetate on nitration with acetic anhydride or acetic acid and copper nitrate.

The results of these nitrations are summarised in the table.

Some difficulty was encountered in the hydrolysis of *p*-nitrobenzylidene diacetate by the method of *Org. Synth.*, Coll. Vol. II, p. 441. It has been found possible to hydrolyse nitrobenzylidene diacetates in high yields by means of magnesium hydroxide suspensions. Alkaline hydrolysis of aldehyde diacetates is not normally feasible as the high concentration of alkali which must be present initially to ensure complete hydrolysis leads to condensation of the aldehyde formed in the early stages of the hydrolysis. It has been found that if the hydrolysis of nitrobenzylidene diacetates is carried out at 100° with increasing concentrations of sodium hydroxide, the Cannizzaro reaction becomes appreciable when the alkali concentration reaches about 0·01N. (pH about 12 at 24°). Condensation could be avoided by adding the alkali at such a rate that the critical pH is never reached and this can be conveniently achieved by hydrolysing these diacetates with magnesium hydroxide suspensions, since the pH of its pure aqueous suspension is about 10·4 (at 24°).

Nitration of cinnamic acid, ethyl cinnamate, benzylidene diacetate and acetophenone.

Reactants.	Conditions.	Products.
1. Cinnamic acid : HNO_3	3 hrs., <10°	49% *o*- + 39% *p*-nitrocinnamic acid
2. „ HNO_3–H_2SO_4	4 hrs., <20°	50% *o*- + 39% *p*-nitrocinnamic acid
3. „ HNO_3–AcOH	4 hrs., <20°	Unchanged
4. Ethyl cinnamate : HNO_3	4 hrs., <20°	56% *o*- + 27% *p*-nitrocinnamic acid
5. „ HNO_3–H_2SO_4	4 hrs., <20°	43% *o*- + 42% *p*-nitrocinnamic acid
6. Cinnamic acid : Ac_2O–$Cu(NO_3)_2$	Uncontrolled	68% *o*- + 15% *p*-nitrobenzoic acid
7. Benzylidene diacetate : Ac_2O–$Cu(NO_3)_2$	„	52% *p*-nitrobenzylidene diacetate
8. „ „ AcOH–$Cu(NO_3)_2$	5 hrs., reflux	79% „ „
9. Benzaldehyde : AcOH–$Cu(NO_3)_2$	„	79% „ „
10. Benzylidene diacetate : Ac_2O–HNO_3	118°	43% *o*-nitrobenzaldehyde + 26% *p*-nitrobenzoic acid
11. „ „ „	4 hrs., <20°	41% *o*-nitrobenzaldehyde
12. „ „ AcOH–HNO_3	Uncontrolled	96% benzoic acid
13. „ „ HNO_3–H_2SO_4	3 hrs., <15°	33% *o*- + 43% *m*-nitrobenzaldehyde
14. Benzaldehyde : HNO_3–H_2SO_4	4 hrs., <15°	80% *m*- + little *o*-nitrobenzaldehyde
15. Acetophenone : AcOH–$Cu(NO_3)_2$	5 hrs., reflux	42% *p*-nitrobenzylidene diacetate

EXPERIMENTAL.

(All m p s are uncorrected.)

1. *Nitration of Cinnamic Acid with Nitric Acid Alone.*—Finely powdered cinnamic acid (30 g.) was added during 1 hour to vigorously stirred nitric acid (150 ml.; *d* 1·52) and the mixture stirred for a further 2 hours, the temperature being maintained below 10° by external cooling. The resulting paste was stirred into water (2·5 l.) and filtered, and the product washed free from mineral acid with cold water.

The air-dried product (38 g.) was suspended in ethanol (400 ml.), sulphuric acid (15 ml.; *d* 1·84) added, and the whole refluxed until dissolution was complete. The resulting solution was cooled to 0° and kept overnight in the refrigerator. The ethyl *p*-nitrocinnamate which had separated was filtered off and washed with cold ethanol (50 ml.), the filtrate and washings being combined. The ester, after recrystallisation from ethanol, was boiled with ethanol (200 ml.) and sulphuric acid [50 ml. (*d* 1·84) +350 ml. of water] for 8 hours. After addition of water (500 ml.) the precipitated acid was filtered off, and purified by dissolution in sodium carbonate solution, filtration, and reprecipitation by hydrochloric acid. Recrystallisation of the product from ethanol gave *p*-nitrocinnamic acid (15·2 g., 39%), m. p. 286° (Müller, *Annalen*, 1882, **212**, 126, gives m. p. 286°).

Hydrolysis of the filtrate was achieved by the addition of water (500 ml.) and refluxing for 12 hours. The *o*-nitrocinnamic acid was precipitated by pouring the mixture into water and purified as in the case of the *p*-nitro-acid, to give an acid (19·2 g., 49%), m. p. 240° (Müller, *loc. cit.*, gives m. p. 240°).

2. *Nitration of Cinnamic Acid with Nitric and Sulphuric Acids.*—Cinnamic acid (30 g.), dissolved in sulphuric acid (250 ml.; *d* 1·84) was nitrated by the addition of nitric acid (11 ml.; *d* 1·52) during an hour, and stirring for a further 3 hours, the temperature being kept below 20°. Isolation of the mixed acids by precipitation with water, filtration, and washing gave a product which was separated as before to give *p*- (15·5 g., 39%; m. p. 286°) and *o*-nitrocinnamic acid (19·5 g., 50%; m. p. 240°).

3. *Nitration of Cinnamic Acid with Acetic and Nitric Acids.*—Addition of nitric acid [11 ml. (*d* 1·52) or 50 ml. (*d* 1·52)] to cinnamic acid (30 g.) in glacial acetic acid (250 ml.) afforded only unchanged cinnamic acid.

4. *Nitration of Ethyl Cinnamate with Nitric Acid Alone.*—Ethyl cinnamate (50 g.) was nitrated by adding it slowly to cooled nitric acid (250 ml.; *d* 1·52) and stirring for a further 3 hours, at <20°. The mixed nitro-esters were isolated by pouring the mixture into water (2·5 l.), filtration, and washing. Separation was achieved by dissolving the mixture in ethanol (500 ml.), cooling to 0°, and allowing the *p*-ester to separate overnight in the refrigerator. Hydrolysis by the methods already described and purification of the acids gave *p*- (15 g., 27%; m. p. 286°) and *o*-nitrocinnamic acid (31 g., 56%; m. p. 240°).

5. *Nitration of Ethyl Cinnamate with Sulphuric and Nitric Acids.*—Nitration of ethyl cinnamate (50 g.) dissolved in sulphuric acid (150 ml.; *d* 1·84) as in (2) above, using nitric acid (20 ml.; *d* 1·52), gave *p*- (23 g., 42%; m. p. 286°) and *o*-nitrocinnamic acid (24 g., 43%; m. p. 240°).

6. *Nitration of Cinnamic Acid with Acetic Anhydride and Copper Nitrate.*—Nitration in acetic anhydride with hydrated copper nitrate, warming to 65—70°, and allowing the reaction to proceed spontaneously afforded only *o*- and *p*-nitrobenzoic acids. Under these experimental conditions *o*- and *p*-nitrocinnamic acids are oxidised to the corresponding nitrobenzoic acids. At 20° unchanged cinnamic acid and only 10% of *o*- and *p*-nitrocinnamic acid were obtained.

Oxidation of nitrocinnamic acids to nitrobenzaldehydes. o-Nitrocinnamic acid (10 g.) was dissolved in a solution of sodium carbonate (6 g.) in water (750 ml.), benzene (200 ml.) added, and the mixture cooled to 10° by addition of ice and external cooling. Oxidation was achieved by the addition of potassium permanganate solution (250 ml.; 6%) with vigorous stirring to ensure thorough mixing, the temperature being kept below 10° by the addition of ice. Stirring was continued for a further hour, the product filtered, and the manganese dioxide washed with benzene (50 ml.). The benzene layer was separated and the aqueous layer extracted with benzene (2 × 50 ml.) which was added to the main extract. After being washed with water, the benzene extract was dried, and the benzene distilled off. The residue was dissolved in toluene (10 ml.), light petroleum (70 ml.; b. p. 40—60°) added, and the solution cooled to 0°, to give *o*-nitrobenzaldehyde (5 g., 64%), m. p. and mixed m. p. 43° (oxime, m. p. 103°; acetone condensed with it in presence of sodium hydroxide to give indigo, soluble in chloroform). Extraction of the acidified aqueous layer with ether and removal of the ether gave *o*-nitrobenzoic acid, (1·7 g., 20%), m. p. and mixed m. p. 146°.

Oxidation of *p*-nitrocinnamic acid under identical conditions gave *p*-nitrobenzaldehyde (5·8 g., 74%), m. p. and mixed m. p. 106° (oxime, m. p. 132°), and *p*-nitrobenzoic acid (1·3 g., 15%), m. p. and mixed m. p. 237°.

7. *Nitration of Benzylidene Diacetate with Acetic Anhydride and Copper Nitrate.*—Benzaldehyde (12 g.) and acetic anhydride (60 g.) were stirred together, and 5 drops of sulphuric acid (*d* 1·84) added to catalyse the formation of the diacetate. After a further 15 minutes' stirring to complete the reaction, hydrated copper nitrate (30 g.) was added, the mixture warmed to 65°, and the vigorous reaction allowed to proceed spontaneously (see note below). When the temperature had fallen to 80°, water (500 ml.) and sulphuric acid [25 ml. (*d* 1·84) + 4 parts water] were added and the mixture set aside overnight. The precipitated *p*-nitrobenzylidene diacetate was filtered off, washed free from acid with water, and recrystallised from aqueous ethanol to give *p*-nitrobenzylidene diacetate (15 g., 52%), m. p. and mixed m. p. 122°. Hydrolysis of the diacetate is described later. Note: addition of copper nitrate to acetic anhydride may lead to an exothermic reaction.

Attempts to nitrate benzylidene diacetate in acetic anhydride solution with hydrated copper nitrate at <20° during 7 hours yielded only unchanged diacetate. Benzaldehyde is not nitrated by copper nitrate in acetic acid at <20°.

8. *Nitration of Benzylidene Diacetate with Acetic Acid and Copper Nitrate.*—Benzaldehyde (106 g.) was converted by acetic anhydride (250 ml.) and sulphuric acid (5 ml.; *d* 1·84) into the diacetate, which was isolated by precipitation with water. The separated diacetate was drained at the pump, dissolved in acetic acid (1 l.), and nitrated by refluxing it for 5 hours with hydrated copper nitrate (300 g.). The product was isolated as before, and the *p*-nitrobenzylidene diacetate (200 g., 79%) was hydrolysed by the method of *Org. Synth.*, Coll. Vol. II, p. 441, to give *p*-nitrobenzaldehyde (110 g., 73% based on the benzaldehyde taken), m. p. and mixed m. p. 106° (phenylhydrazone m. p. 156°; oxidation with alkaline permanganate gave *p*-nitrobenzoic acid, m. p. and mixed m. p. 237°).

Nitration has also been effected to give similar yields of diacetate and aldehyde by adding the acetic acid and copper nitrate to the acetic anhydride solution of the aldehyde without isolating the diacetate, and this is the most satisfactory method.

9. *Nitration of Benzaldehyde with Acetic Acid and Copper Nitrate, without Intermediate Diacetate Formation.*—Benzaldehyde (25 g.) was refluxed with glacial acetic acid (200 ml.) and hydrated copper nitrate (60 g.) for 5 hours, and the product poured into water, made alkaline with aqueous ammonia and then just acid to litmus with dilute sulphuric acid. The precipitate, on recrystallisation from aqueous ethanol, gave *p*-nitrobenzylidene diacetate (7 g., 12%), m. p. and mixed m. p. 122°.

Reaction between Benzaldehyde and Acetic Acid.—Benzaldehyde (12 g.), glacial acetic acid (60 g.), and sulphuric acid (0·5 ml.; *d* 1·84) were stirred together for periods up to 3 hours at room temperature or up to 30 minutes at the b. p. of the mixture. In no case was benzylidene diacetate obtained on dilution with water, benzaldehyde separating in all cases; there was no evidence of appreciable reaction from time–temperature measurements, typical results being:—

	Temperature.	
Time, min.	Mixture as above.	Acetic acid replaced w./w. by acetic anhydride.
0	18°	18°
0·25	20	50
15	19·5	35

The use of mixtures of acetic acid and anhydride led in all cases to incomplete formation of benzylidene diacetate.

Use of Other Metal Nitrates.—Nitrations of benzylidene diacetate (21 g.) in acetic acid (100 ml.) using various metal nitrates under the conditions previously described were carried out with the following results:

Metal nitrate and wt. (g.) used.		Yield of *p*-nitrobenzylidene diacetate.		Metal nitrate and wt. (g.) used.		Yield of *p*-nitrobenzylidene diacetate.	
		Wt. (g.).	%.			Wt. (g.).	%.
Zinc,	30	6·0	23	Cobalt,	35	1	4
Ferric,	40	5·0	19	Calcium,	25	0	0
Bismuth,	50	5·0	19	Lead,	50	0	0
Nickel,	35	3·0	12	Sodium,	25	deflagration	
Magnesium,	30	2·0	8				

10. *Nitration of Benzylidene Diacetate with Acetic Anhydride and Nitric Acid.*—Benzaldehyde (120 g.) was added to acetic anhydride (500 ml.), and sulphuric acid (10 ml.; *d* 1·84) added slowly with vigorous stirring. The solution was stirred for a further 30 minutes and nitric acid (200 ml.; *d* 1·42) added at the rate of 25 drops per minute, the vigorous reaction maintaining the temperature at 118°. More nitric acid (50 ml.) was then added more rapidly, and the mixture then allowed to cool and poured into a large excess of water. The separated material was filtered off, washed with cold water, and refluxed with ethanol (400 ml.), water (400 ml.), and sulphuric acid (40 ml.; *d* 1·84) for 1 hour. The product was then rapidly steam-distilled to leave a residue of *p*-nitrobenzoic acid (49 g., 26%), m. p. and mixed m. p. 237° (*p*-nitrobenzyl ester m. p. 167°). Extraction of the distillate with ether and removal of the ether gave

a residue which after crystallisation from toluene and 4 volumes of light petroleum (b. p. 40—60°) gave *o*-nitrobenzaldehyde (74 g., 43%), m. p. 42—43° (oxidised by alkaline permanganate to *o*-nitrobenzoic acid, m. p. 147°; acetone condensed in presence of sodium hydroxide to give indigo, soluble in chloroform).

11. *Nitration of Benzylidene Diacetate with Acetic Anhydride and Nitric Acid at Low Temperatures.*—Benzaldehyde (12 g.), dissolved in acetic anhydride (100 ml.), was nitrated by the slow addition of nitric acid (30 ml.; *d* 1·52) with rapid stirring and external cooling, the temperature being kept at <20°. After a further 3 hours' stirring the nitration mixture was set aside at room temperature overnight. The product was poured into water (2 l.), and the separated solid filtered off, washed free from acid and crystallised from toluene–light petroleum, to give *o*-nitrobenzaldehyde (6 g., 41%), m. p. and mixed m. p. 42—43°. In this preparation hydrolysis of the diacetate occurred during isolation, and the above method represents the most convenient method of preparation of *o*-nitrobenzaldehyde by direct nitration of benzaldehyde.

12. *Nitration of Benzylidene Diacetate with Acetic and Nitric Acids.*—Attempts to nitrate benzylidene diacetate in acetic acid at elevated temperatures led to the formation of benzoic acid, whilst at <20° there was no nitration during 2 days.

13. *Nitration of Benzylidene Diacetate with Sulphuric and Nitric Acids.*—Nitration of benzylidene diacetate (21 g.), dissolved in sulphuric acid (100 ml.; *d* 1·84), with nitric acid (10 ml.; *d* 1·52) at <15° led to *o*- (5 g., 33 %) m. p. 42°, and *m*-nitrobenzaldehyde (6·5 g., 43%), m. p. and mixed m. p. 58°. Increase in the proportion of sulphuric acid or the use of mixed acid for the nitration led to the formation of *m*-nitrobenzaldehyde as the main product, hydrolysis of the diacetate occurring before nitration.

14. *Preparation of* m-*Nitrobenzaldehyde.*—Nitration of redistilled benzaldehyde (106 g.), dissolved in sulphuric acid (300 ml.; *d* 1·84), with mixed acid [70 ml. of nitric (*d* 1·52) + 150 ml. of sulphuric acid (*d* 1·84)] at <15° gave *m*-nitrobenzaldehyde (121 g., 80%), m. p. and mixed m. p. 58°. Small amounts (*ca.* 5 g.) of impure *o*-nitrobenzaldehyde were isolated from the acid liquors by ether-extraction, but the product was extremely difficult to purify.

15. *Nitration of Acetophenone with Acetic Acid and Copper Nitrate.*—Acetophenone (25 g.) was refluxed for 5 hours with acetic acid (250 ml.) and hydrated copper nitrate (60 g.), and the mixture poured into a large excess of water and set aside overnight. The product was made alkaline with aqueous ammonia and then just acid with dilute sulphuric acid, and the precipitate filtered off, washed with water, and recrystallised from aqueous ethanol to give *p*-nitrobenzylidene diacetate (22 g., 42%), m. p. and mixed m. p. 122°.

Reaction Mechanism.—Benzoylformic acid (5 g.) was refluxed with acetic anhydride or acid (50 ml.) and hydrated copper nitrate (10 g.). Pouring the mixture into water gave *p*-nitrobenzylidene diacetate (3·1 g.; 2·2 g.), m. p. and mixed m. p. (after crystallisation from ethanol) 122°.

Benzoylformic acid (5 g.) was refluxed for 2 hours with acetic anhydride (50 ml.) and one drop of sulphuric acid, or glacial acetic acid (50 ml.). Benzylidene diacetate (3 g.; m. p. and mixed m. p. 46°) and benzaldehyde (2·2 g., identified as 2 : 4-dinitrophenylhydrazone) respectively were obtained on pouring the mixtures into water.

Oxidation of o- *and* p-*Nitrotoluenes.*—Oxidation of *p*-nitrotoluene by the method of *Org. Synth.*, Coll. Vol. II, p. 441, gave *p*-nitrobenzylidene diacetate in 46% yield, whilst oxidation of *o*-nitrotoluene gave 20—25% yields of the *o*-nitro-diacetate and always led to the formation of much tar.

Hydrolysis of Diacetates.—Difficulty was encountered in the acid hydrolysis of *p*-nitrobenzylidene diacetate by the method of *Org. Synth.* but rapid and complete hydrolysis of diacetates was effected as follows. The diacetate (50 g.) was refluxed with a 2·5% suspension (800 ml.) of magnesium hydroxide for 2 hours. The product was cooled, the excess of magnesium hydroxide dissolved in dilute sulphuric acid (50—60 ml.; 5N.), and the mixture chilled in ice. The aldehyde which separated was filtered off and recrystallised. Additional small amounts of aldehyde could be recovered by ether-extraction of the mother-liquors. Yields of 90—95% have been obtained.

"Milk of magnesia," diluted with 2½ parts (vol.) of water, was most suitable, as the particles are very finely dispersed but the suspension is free from any added dispersing agent.

Thanks are due to Messrs Chas. H. Phillips Chemical Co. for gifts of "Milk of magnesia."

ACTON TECHNICAL COLLEGE, HIGH ST., W.3. [*Received, October 18th*, 1949.]

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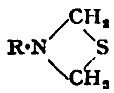
48. *The Action of Hydrogen Sulphide on Certain Methyleneimines. Part I.*

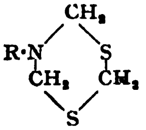
By ERIC R. BRAITHWAITE and JOHN GRAYMORE.

Hydrogen sulphide reacts with *N*-methylene*cyclo*hexylamine in the presence of formaldehyde to give N-cyclo*hexylthioformaldine*, but in the absence of formaldehyde the main product is 5-cyclo*hexyl*-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine*. With methylenebenzylamine, hydrogen sulphide and formaldehyde give a single product, 3 : 5-dibenzyltetrahydro-1-thia-3 : 5-diazine. This difference can be ascribed to the dimeric structure of methylenebenzylamine.

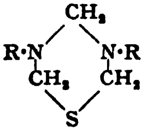
WOHL (*Ber.*, 1886, **19**, 2345) obtained a product from formaldehyde saturated with hydrogen sulphide by adding methylamine. He described it as methylthioformaldin (II; R = CH_3). Le Fèvre (*J.*, 1935, 865) obtained a four-membered ring compound formulated as (I; R = CH_3) by first saturating an aqueous solution of methylamine with hydrogen sulphide and then adding formaldehyde solution; the author observed that on dissolving his product in warm acetone, conversion into Wohl's methylthioformaldin took place. No other six-membered ring compound of the type described by Wohl was obtained.



(I.)



(II.)

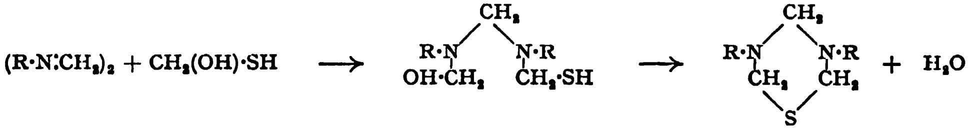


(III.)

We considered that it should be possible to obtain compounds of types (I), (II), and (III) from suitable amines, formaldehyde, and hydrogen sulphide. Formaldehyde is known to condense with *cyclo*hexylamine (*J.*, 1947, 1118) and with benzylamine to give readily crystallisable methyleneimines. As the formation of a thialdine in the Wohl–Le Fèvre reaction is probably preceded by the formation of a methyleneimine, it seemed reasonable to use the methyleneimines as starting points. Consequently, a study of the reaction was made with formaldehyde and hydrogen sulphide on the one hand, and *N*-methylene*cyclo*hexylamine or *N*-methylenebenzylamine on the other.

Aqueous-alcoholic solutions of the methyleneimines were accordingly treated with formaldehyde. The mixtures were cooled to keep the temperature below 25°, and a stream of hydrogen sulphide passed in. In each case a single crystalline product separated in excellent yield, but whereas *N*-methylene*cyclo*hexylamine gave a *thioformaldine* of type (I; $R = C_6H_{11}$), *N*-methylenebenzylamine gave 3 : 5-*dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine* (III; $R = CH_2Ph$).

It had been noted that, although both methyleneimines can be precipitated from alcoholic solution by the addition of water, yet *N*-methylene*cyclo*hexylamine was not precipitated from alcoholic solution even by the addition of excess of formaldehyde (40% formalin). *N*-Methylenebenzylamine on the other hand was precipitated. These observations seemed to indicate that the former, a monomer, adds formaldehyde to give in all probability $C_6H_{11}N(CH_2{\cdot}OH)_2$, which condenses with hydrogen sulphide to give (I; $R = C_6H_{11}$). *N*-Methylenebenzylamine, a dimer, could not combine with formaldehyde and it is therefore probable that the dibenzyl compound (III; $R = CH_2Ph$) is produced as follows:



An aqueous-alcoholic solution of *N*-methylene*cyclo*hexylamine in the absence of formaldehyde reacted exothermally with hydrogen sulphide. With the temperature kept below 25°, two crystalline compounds were eventually obtained, namely, 5-cyclo*hexyl*-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine* similar to the thioformaldine described by Wohl (II; $R = C_6H_{11}$) and a smaller quantity of type (I).

Repeated attempts to make 5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine from (I) by the action of hydrogen sulphide in the presence of formaldehyde were unavailing, so it might well be that (I) and (II) ($R = C_6H_{11}$) are formed independently from the methyleneimine by condensation with $CH_2(OH){\cdot}SH$ and $CH_2(OH){\cdot}S{\cdot}CH_2{\cdot}SH$, respectively. The first stage in the reaction of hydrogen sulphide with the methyleneimine is undoubtedly the partial breakdown of the latter to give *cyclo*hexylamine,

$$C_6H_{11}{\cdot}N{:}CH_2 + H_2O + H_2S \longrightarrow C_6H_{11}{\cdot}NH_2 + CH_2(OH){\cdot}SH$$

since cyclo*hexylamine thiosulphate* slowly separates from the residual liquor.

When hydrogen sulphide was passed into the aqueous-alcoholic solution of *N*-methylene*cyclo*hexylamine without temperature control, the temperature rose rapidly with the separation of a voluminous non-nitrogenous solid. Its melting point and general properties indicated that it was the compound which Wohl obtained by the action of hydrogen sulphide upon an aqueous or alcoholic solution of hexamine. Wohl assigned to it the formula $(CH_2S)_n$. Analyses of the compound now obtained did not agree with his findings. It is hoped to deal with this problem later.

After removal of the bulky insoluble precipitate, the filtrate was allowed to evaporate spontaneously, leaving a residue of *cyclo*hexylamine thiosulphate. Marrin, Achterhof, Conway, and Boord (*J. Amer. Chem. Soc.*, 1931, 53, 2682) showed that the hydrosulphides of certain amines oxidised in air to the corresponding thiosulphates. The thiosulphates of *cyclo*hexylamine and *benzylamine* separated in considerable yields when air was blown through an alcoholic solution of the amine saturated with hydrogen sulphide.

All three thioformaldines decompose when heated with hydrochloric acid—(I) rapidly, (II) and (III) slowly—to give trithioformaldehyde (cf. Le Fèvre, *J.*, 1935, 865). Similarly, they all decompose when heated under reflux in alcoholic solution in a stream of hydrogen sulphide to give the non-nitrogenous compound described above.

EXPERIMENTAL.

cyclo*Hexylthioformaldine* (3-cyclo*Hexyl*-1-*thia*-3-*azetidine*).—*N*-Methylene*cyclo*hexylamine (5·0 g.), freshly prepared and recrystallised from ethanol, was dissolved in alcohol (50 c.c.), and formaldehyde (25 c.c. of a 40% solution) added. After a few minutes, hydrogen sulphide was passed in for 10 minutes, the temperature being kept below 25°. The resulting solid was removed. The process was repeated until no further yield (total, 4·3 g.) was obtained. The *thioformaldine* crystallised from acetone in needles, m. p. 118—120° (Found: C, 60·6; H, 9·4; N, 8·9. $C_8H_{15}NS$ requires C, 61·1; H, 9·5; N, 8·9%). It was soluble in acetone, methanol, benzene, chloroform, or light petroleum. A solution in ethanol gave with an alcoholic solution of hydrogen chloride a crystalline *hydrochloride*, m. p. >120° (decomp.) (Found: N, 7·17; Cl, 18·0. $C_8H_{16}NClS$ requires N, 7·2; Cl, 18·3%).

The mother compound (0·4 g.) was dissolved in aqueous alcohol and heated under reflux (10 minutes). The solution was cooled, and water added, whereupon glistening needles were obtained which on recrystallisation gave 5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine, m. p. and mixed m. p. 58°.

*cyclo*Hexylthioformaldine (1 g.), dissolved in dilute hydrochloric acid (50 c.c.) and heated under reflux, rapidly decomposed with evolution of formaldehyde and separation of trithioformaldehyde in needles (m. p. and mixed m. p. 216°). The mother-liquor after cooling and removal of the solid gave, with benzoyl chloride and sodium hydroxide, benzo*cyclo*hexylamide (m p. and mixed m. p. with an authentic specimen 160°).

5-cyclo*Hexyl*-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine*.—Methylene*cyclo*hexylamine (26 g.) was dissolved in ethanol (50 c.c.), and water was added until the mixture remained faintly opaque. Hydrogen sulphide was passed in at 0° for 1—2 hours. The precipitate (5·8 g.) which separated was recrystallised first from aqueous alcohol and finally from ethanol, forming long needles, m. p. 58°, of the *dithia-azine* (Found: C, 53·35; H, 8·5; N, 7·1; S, 31·0. $C_9H_{17}NS_2$ requires C, 53·2; H, 8·4; N, 6·9; S, 31·5%). It was insoluble in water, moderately soluble in acetone, and soluble in benzene or chloroform.

The filtrate from the first precipitate slowly deposited needles, m. p. 105—106° (1 g.); these recrystallised from acetone in needles and were identified as *cyclo*hexylthioformaldine (m. p. and mixed m. p. 118°). The filtrate from the above was distilled into 2N-hydrochloric acid and gave *cyclo*hexylamine hydrochloride (m. p. and mixed m. p. 204—205°).

5-cyclo*Hexyl*-5 : 6-*dihydro*-1 : 3-*dithia*-5-*azine hydrochloride* was obtained by passing hydrogen chloride through a solution of the parent compound in light petroleum, with cooling. It separated from ethanol in white needles, m. p. 185° (Found: Cl, 14·9. $C_9H_{18}NClS_2$ requires Cl, 14·6%).

The hydrochloride (0·75 g.) was dissolved in concentrated hydrochloric acid (10 c.c.), and the solution heated under reflux for 3 hours. A white solid (0·28 g.) separated and after recrystallisation from acetone was identified as trithioformaldehyde, needles, m. p. and mixed m. p. 216°.

cyclo*Hexylamine Thiosulphate*.—Methylene*cyclo*hexylamine (18 g.) was dissolved in ethanol, and the solution saturated with hydrogen sulphide for 5 hours, the temperature rising to 45°. The solid deposited was repeatedly washed with hot ethanol until no further solution appeared to take place. The solution was filtered hot, and, on cooling, silvery white plates of cyclo*hexylamine thiosulphate* separated, m. p. 198° (decomp.). It gave the usual reactions of thiosulphates (Found: C, 45·9; H, 8·8; N, 8·9. $C_{12}H_{28}O_3N_2S_2$ requires C, 46·15; H, 8·9; N, 8·9%). The insoluble residue, m. p. 175°, was nitrogen-free but its structure has not yet been determined. The thiosulphate was obtained directly by saturating an ethanolic solution of *cyclo*hexylamine with hydrogen sulphide and passing air through the mixture until no further precipitate was obtained. Recrystallised from ethanol it gave white leaflets, m. p. 198° (decomp.) [Found: 0·9995 g. = 31·9 c.c. of 0·01N-iodine solution. $(C_6H_{11}{\cdot}NH_2)_2S_2O_3$ requires 31·8 c.c.].

3 : 5-*Dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine*.—Methylenebenzylamine (5·0 g.) was dissolved in ethanol (50 c.c.), and formaldehyde (15 c.c. of a 40% solution) which had previously been saturated with hydrogen sulphide was added. A stream of hydrogen sulphide was passed in until the temperature rose to 25°. The solution became opaque after 15 minutes; it was set aside for 24 hours, and the crystals which separated were removed by filtration, and then recrystallised from ethanol in long needles, m. p. 92° (Found: C, 71·8; H, 7·05; N, 9·4, 9·5; S, 10·8. $C_{17}H_{20}N_2S$ requires C, 71·8; H, 7·0; N, 9·8; S, 11·0%). This 3 : 5-*dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine* was dissolved in light petroleum, and the solution saturated with hydrogen chloride. The white *dihydrochloride* which separated was removed and crystallised from ethanol; it had m. p. 130—140° (decomp.) (Found: Cl, 20·1. $C_{17}H_{22}N_2Cl_2S$ requires Cl, 19·9%). When heated under reflux for 3 hours with concentrated hydrochloric acid, the parent substance (0·75 g.) gave trithioformaldehyde (0·1 g.).

Benzylamine Thiosulphate.—Benzylamine (10 g.) was dissolved in ethanol (40 c.c.), and the solution saturated with hydrogen sulphide. Air was passed through the mixture and *benzylamine thiosulphate* slowly separated in silvery leaflets (10 g.). These crystallised from ethanol in leaflets, m. p. 182° (decomp.) [Found: 0·9995 g. = 30·2 c.c. of 0·01N-iodine. $(C_6H_5{\cdot}CH_2{\cdot}NH_2)_2S_2O_3$ requires 30·3 c.c.].

Analyses were by Drs. Weiler and Strauss.

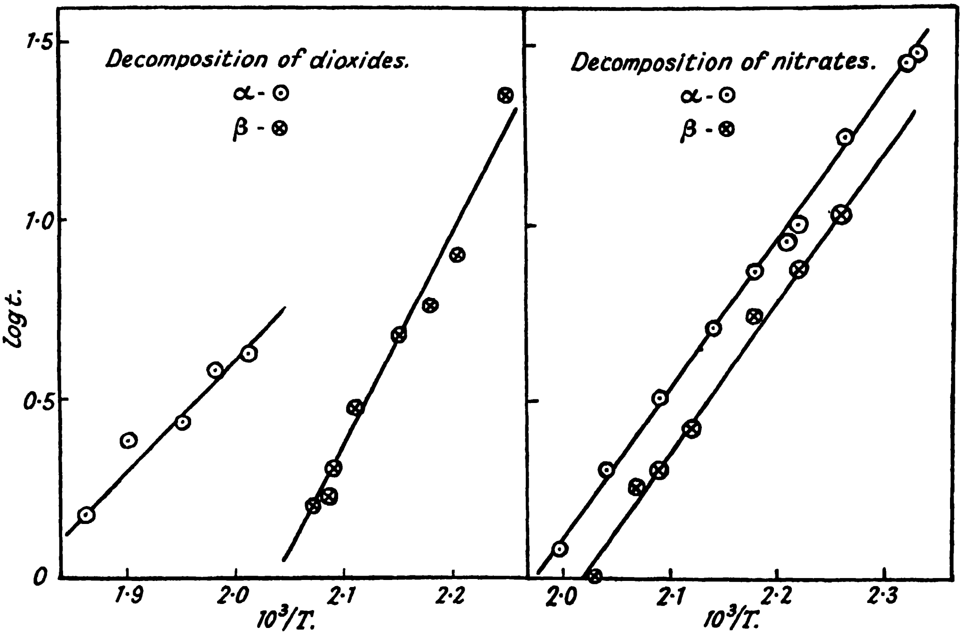
PLYMOUTH AND DEVONPORT TECHNICAL COLLEGE, PLYMOUTH. [*Received, October 12th*, 1949.]

49. *Geometrical Isomerism of the Dioxides of Diphenylpiperazine.*

By G. M. Bennett and (Mrs.) Erika Glynn.

Diphenylpiperazine is oxidised by hydrogen peroxide to two isomeric di-*N*-oxides. The α-isomeride crystallises as an efflorescent octahydrate and a stable dihydrate which loses its water in a vacuum. The β-isomeride, formed in a proportion of about 1 in 10, is much the more soluble in water. It is isolated in the form $B,H_2O_2,2H_2O$, stable in a vacuum. The salts of these dioxides are usually anhydrous, free from hydrogen peroxide, and of the composition B,2HX. The isomeric hydrochlorides, nitrates, and picrates have been characterised and also the oxalate, sulphate, perchlorate, ferrocyanide, platinichloride and aurichloride of the α-dioxide. All these substances explode when heated, and the times required for explosion at various temperatures have been studied. The stability of its complex with hydrogen peroxide indicates that the β-isomeride has the *cis*-configuration.

Di-*N*-oxides of suitable diamines should exist in diastereoisomeric or *cis-trans*-forms analogous to those of the dithian dioxides (Bell and Bennett, *J.*, 1927, 1788). In order to demonstrate this the oxidation of 1 : 4-diphenylpiperazine has been examined. Hydrogen peroxide in acetone or glacial acetic acid yielded as the main product the *α-dioxide*, crystallising magnificently from warm water as the *octahydrate*, which, however, rapidly effloresces to the *dihydrate* stable in air. Both hydrates lose their water in a vacuum to give the hygroscopic anhydrous *dioxide*.



From the mother-liquor of the α-dioxide a small quantity of a much more soluble β-*dioxide* was isolated which was found on analysis to have the composition β-dioxide,H_2O_2,$2H_2O$. The presence of hydrogen peroxide was also confirmed by direct tests. These crystals are stable in air and lose neither water nor hydrogen peroxide when kept in a vacuum. Both dioxides are readily reduced to the parent diphenylpiperazine.

The two dioxides give salts which are generally anhydrous and contain no hydrogen peroxide. Pairs of isomeric *hydrochlorides*, *nitrates*, and *picrates* were characterised and in addition the *sulphate*, *oxalate*, *perchlorate*, *ferrocyanide*, *platinichloride*, and *aurichloride* of the α-dioxide.

The two dioxides and all their salts decompose explosively when heated. A study of the temperatures of decomposition showed that for each substance explosion occurred after a particular time (t secs.) of heating at a given temperature (T °K.) where $\log_{10} t = a/T - b$, a and b being constants for the substance. This relationship is illustrated in the figure for observations with the α- and the β-nitrate and with the two dioxides (α-dioxide dihydrate and hydrated β-dioxide–hydrogen peroxide complex). The constants a and b for all the compounds studied are in the table.

Substance.	$10^{-3}a$.	b.	Temperature (° c.) (calc.) for $t = 1$ sec.
α-Oxalate	6·6	11·8	289°
α-Hydrochloride	5·7	10·6	268
α-Aurichloride	4·8	10·6	182
α-Nitrate	4·2	8·3	234
β-Nitrate	4·2	8·5	224
α-Picrate	6·5	13·5	221
β-Picrate	5·8	12·2	207
α-Dioxide dihydrate	3·2	5·8	281
β-Dioxide complex	5·8	12·0	210

It is noticeable that the values of a (slopes of the curves in the figure) are similar for the pairs of isomerides. This is not so for the two dioxides, but the compounds actually examined were in this case not isomeric since only the β-specimen contained combined hydrogen peroxide.

This type of behaviour has been reported more than once before, for example for the decomposition of lead styphnate (Hales, *Trans. Faraday Soc.*, 1933, **29**, 544) and of barium azide (Hervey, *ibid.*, p. 653). The former author records some variation in times before detonation with the size of the crystals. Our specimens were all finely powdered.

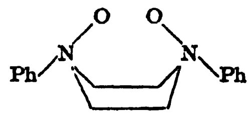
These observations help in characterising the compounds examined and, in the absence of melting points, provide clear evidence of the individuality of the pairs of isomerides studied.

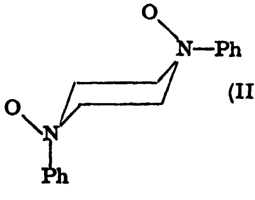
The α-dioxide and its salts are all somewhat more stable than their β-isomerides. The α-dioxide is more sparingly soluble in water (by a factor of the order of 100 : 1) than the β-dioxide, but in 95·6% alcohol the converse is true and the solubilities at 25° were α- 9·1 and β- 1·16% by weight.

Although the α-dioxide forms stable salts of the composition B,2HX, its aqueous solutions are not alkaline but have a pH between 6 and 7. Moreover measurably more N/10-sodium hydroxide is needed to change the colour of phenolphthalein in its presence than in pure water. A similar faintly acidic character was observed by Polonovski, Boulanger, and Taghavi (*Atti del X° Congresso Internazionale di Chimica, Roma,* 15—21, Maggio, 1938, XVI, 3, 303) with dimethylpiperazine dioxide. The formula suggested by these authors for a negative ion produced by the union of an amine oxide and a hydroxyl ion is, however, electronically unsound and we doubt whether the effect under consideration can be explained in terms of normal bonding.

The tenacity with which the molecule of hydrogen peroxide is retained by the β-dioxide is remarkable and may be regarded as significant in connexion with the question of configuration. General considerations such as stability, as indicated by temperatures of decomposition, and solubility in water would suggest that the α-dioxide has the *trans*-configuration. The stable retention of hydrogen peroxide might be due to the attachment of the peroxide molecule by hydrogen bonds simultaneously to both amine oxide oxygen atoms, and this would be expected to be possible in a *cis*- but not in a *trans*-form of the piperazine dioxide. A study of molecular models supports this view. For this purpose we have assumed the following interatomic distances : CH_2-CH_2 1·54; CH_2-N 1·47; $\overset{+}{N}-\overset{-}{O}$ 1·36 A. (compare Sutton, *J.*, 1945, 146). If all the angles in the piperazine ring are taken as tetrahedral, the ring must be puckered and there are several distinct arrangements for each of the *cis*- and *trans*-forms of the dioxide (actually 5 *cis* and 4 *trans*). In the various arrangements of the *trans*-form the distance between the two oxygen atoms is of the order 4—5 A., but in every case the bulky phenyl group or the atoms of the ring are interposed making any bridging by the hydrogen peroxide molecule improbable. On the other hand no such obstruction arises in the various arrangements of the *cis*-dioxide. In one of these (I) the oxygen atoms are less than 2 A. apart (calculated on the above-mentioned assumptions, 1·61 A.), but this particular arrangement would presumably have low stability owing to the close approach of the mutually repellent fields of the two amine oxide groups. The other possible arrangements of the *cis*-dioxide have oxygen atoms at a distance of the order 4—5 A., for example (II) (calculated distance, 4·35 A.). In considering the possible attachment

(I.)





(II.)

of hydrogen peroxide the *X*-ray examination of the crystal structure of the urea–hydrogen peroxide compound by Lu, Hughes, and Giguère (*J. Amer. Chem. Soc.*, 1941, **63**, 1507) is relevant. These authors concluded that the crystal is an assemblage of urea and hydrogen peroxide molecules held together by hydrogen bonds, the hydrogen peroxide molecule retaining the configuration calculated for it by Penney and Sutherland (*Trans. Faraday Soc.*, 1934, **30**, 898) in which the O–H bonds are at 101·5° to the O–O bond but lie in two planes inclined at 106° to each other. A trial with models, taking the O–O distance in hydrogen peroxide to be 1·47 A. (Giguère and Schomaker, *J. Amer. Chem. Soc.*, 1943, **65**, 2025) shows that this hydrogen peroxide molecule can in fact be fitted, with only slight distortion of the angles, to bridge the two oxygen atoms of the *cis*-dioxide in the arrangement (II) with hydrogen bond distances of the order 2·7 A. We therefore conclude that the stability of the hydrogen peroxide complex is strong evidence that the β-dioxide has the *cis*-configuration.

It is evident that the dioxide of dimethylpiperazine should similarly occur in *cis*- and *trans*-forms. Although this substance was described by Polonovski, Boulanger, and Taghavi (*loc. cit.*) no such isomerism was reported. Yet their paper does contain indications of the existence of two forms, and the point requires re-investigation.

While this work was in progress the geometrical isomerism of some diquaternary salts of dimethylpiperazine of the type $\left[\mathrm{RMe}\overset{+}{\mathrm{N}}{<}\genfrac{}{}{0pt}{}{\mathrm{CH_2{\cdot}CH_2}}{\mathrm{CH_2{\cdot}CH_2}}{>}\overset{+}{\mathrm{N}}\mathrm{MeR}\right]\mathrm{X_2}$ was described by Hanby and Rydon (*J.*, 1945, 833). These are analogous to the isomerides described in this paper.

EXPERIMENTAL.

Analyses.—Determinations of carbon, hydrogen, and nitrogen were made by Messrs. Weiler and Strauss. Determinations of peroxidic oxygen were carried out by the method recently described by one of us (Glynn, *Analyst*, 1947, **72**, 248). Explosion temperatures given below are calculated temperatures at which explosion occurs after 1 second.

Oxidation of 1 : 4-*Diphenylpiperazine.*—A mixture of the base (20 g.) dissolved in glacial acetic acid (300 ml.) with hydrogen peroxide (120 g. of 30% aqueous) was kept at 50—70° for 16 hours. The resulting dark red solution gave a copious precipitate of the α-dioxide when neutralised with 10N-sodium hydroxide, but in order to isolate the whole of the products with a minimum contamination with inorganic matter the solution was diluted and evaporated several times at 60° and finally kept over sodium hydroxide in a desiccator until all the acetic acid had been removed. The crude product had a peroxidic oxygen content of 6·8%. This was dissolved in water (500 ml.) at 60°, and the solution on cooling deposited crystals of the hydrated α-dioxide (15 g.). After 2 further crystallisations from water the *diphenylpiperazine α-dioxide octahydrate* was obtained in large well-formed crystals (Found: peroxidic O, 7·78, 7·68%).

Evaporation of the original mother-liquors yielded further small crops of crude α-dioxide, and the solution was finally taken to dryness in a desiccator over potassium hydroxide. A brown oily residue was left which gradually became crystalline (Found, in the crude product: peroxidic O, 13·2, 12·1%). This material was extracted with rectified alcohol, some insoluble inorganic matter being rejected, and after repeated crystallisation from 95% ethanol (charcoal) the β-dioxide was obtained.

Diphenylpiperazine α-Dioxide.—The large crystals from warm water are the octahydrate which effloresces rapidly in air (Found: C, 47·3; H, 8·0; N, 6·8. $C_{16}H_{18}O_2N_2,7{\cdot}7H_2O$ requires C, 47·2; H, 8·3; N, 6·9%. A freshly prepared specimen gave peroxidic O, 7·76; loss over P_4O_{10}, 34·9. $C_{16}H_{18}O_2N_2,8H_2O$ requires peroxidic O, 7·73; H_2O, 34·8%). This substance is sparingly soluble in cold water but more readily soluble in alcohol. 60 Ml. of a 0·16M-solution required 0·26 ml. of N/10-sodium hydroxide for titration with phenolphthalein as indicator, as compared with one drop in a similar volume of pure water.

This octahydrate crystallises magnificently in the orthorhombic system with $a : b : c =$ 0·5639 : 1 : 0·7067. The habit is prismatic with the form *q*(011) elongated along the *c* axis, the prisms being terminated by the form *m*(110). Barker classification angles: *cr*(001) : (101) = 51°25′; *am*(100) : (110) = 29°25′; and *bq*(010) : (011) = 54°45′. The extinction is straight on the prism faces and one optic axis emerges nearly perpendicular to *m*.

The anhydrous *diphenylpiperazine α-dioxide* is obtained as a white hygroscopic powder by dehydrating the octahydrate *in vacuo* over phosphoric anhydride (Found: C, 69·8; H, 6·9. $C_{16}H_{18}O_2N_2$ requires C, 71·1; H, 6·5%). Exposed to the atmosphere this substance absorbs water (2 mols.) smoothly in 2 hours without any intermediate break in the process. The *dihydrate* so obtained is also formed by the efflorescence of the octahydrate in air (Found: C, 62·7; H, 7·25; N, 9·4; peroxidic O, 10·2%. $C_{16}H_{18}O_2N_2,2H_2O$ requires C, 62·7; H, 7·25; N, 9·2; peroxidic O, 10·4%). It is quite stable in air and is obtained in well-formed crystals when any of the forms of the α-dioxide is recrystallised from 95% ethanol. It explodes at 281° (corr.). Its solubility in 95·6% alcohol at 25° is 9·15 wt.-% of anhydrous dioxide.

The crystals of dihydrate belong to the holohedral class of the monoclinic system with $a : b : c =$ 2·041 : 1 : 1·500 and $\beta = 87°4'$. The habit is usually tabular with *c*(001) large, *a*(100) absent or small, and the pyramid faces *o*(111) and *p*($\bar{1}$11) prominent. Barker classification angles: *cr*(001) : (101) = 35°15′; *ra*(101) : (100) = 51°49′; *am*(100) : (110) = 63°52′ and *bq*(010) : (011) = 33°43′. The extinction on *c* is diagonal.

Reduced in aqueous hydrochloric acid with zinc dust the α-dioxide dihydrate yields the parent diphenylpiperazine base.

The *dihydrochloride* forms a colourless crystalline powder readily soluble in cold water but sparingly in alcohol and exploding at 268° (corr.) (Found: C, 55·1; H, 5·5; N, 8·7; HCl by titration, 21·4. $C_{16}H_{20}O_2N_2Cl_2$ requires C, 55·1; H, 5·8; N, 8·2; HCl, 21·3%). The *sulphate* is a white microcrystalline powder sparingly soluble in cold water or alcohol (Found: C, 52·1; H, 5·4; H_2SO_4 by titration, 26·9. $C_{16}H_{20}O_6N_2S$ requires C, 52·3; H, 5·4; H_2SO_4, 26·6%). The *dipicrate* crystallises from alcohol in yellow needles with a straight extinction, sparingly soluble in alcohol but more so in water, and exploding at 221° (corr.) (Found: C, 46·2; H, 3·4; N, 15·0. $C_{28}H_{24}O_{16}N_8$ requires C, 46·2; H, 3·3; N, 15·4%). The *dinitrate* is a white powder consisting of microscopic prismatic crystals having a high double refraction and an oblique extinction. It is sparingly soluble in water and explodes at 234° (corr.) (Found: C, 48·3; H, 4·7; N, 15·3. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·1; N, 14·2%). The *oxalate* is a white microcrystalline powder sparingly soluble in cold water and exploding at 289° (corr.) (Found: C, 59·4; H, 5·5. $C_{18}H_{20}O_6N_2$ requires C, 59·8; H, 5·6%). The *monoperchlorate* was obtained, even in presence of an excess of perchloric acid, as a sparingly soluble microcrystalline powder exploding with a bright flash when heated (Found: C, 51·0; H, 4·8; N, 7·6; $HClO_4$ by titration, 27·5. $C_{16}H_{19}O_6N_2Cl$ requires C, 51·8; H, 5·2; N, 7·6; $HClO_4$, 27·1%). The *platinichloride* is a yellow sparingly soluble precipitate (Found: Pt, 28·6. $C_{16}H_{20}O_2N_2Cl_6Pt$ requires Pt, 28·7%). The *aurichloride* was obtained as a sparingly soluble yellow precipitate when gold chloride solution was added to the aqueous solution of the α-dioxide whether neutral or acid. It decomposes explosively at 182° (corr.) (Found: C, 31·4; H, 3·3; Cl, 22·2; Au, 32·9, 32·2. $C_{16}H_{19}O_2N_2Cl_4Au$ requires C, 31·5; H, 3·1; Cl, 23·2; Au, 32·3%). On the other hand, when the solution of the α-dioxide was added to an excess of gold chloride in aqueous hydrochloric acid, the precipitate, although very little different in composition (Found: Au, 31·7%), was extremely explosive, detonating on scratching or on heating to 90°. For analysis it was moistened and treated with sulphur dioxide, then dried, and ignited. The *ferrocyanide* forms sparingly soluble yellow needles with a straight extinction, which appear to be a dihydrate (Found: C, 56·7; H, 5·6; N, 17·9. $C_{38}H_{44}N_{10}O_6Fe$ requires C, 57·5; H, 5·7; N, 17·7%).

Diphenylpiperazine β-Dioxide.—The substance isolated from the final mother-liquors of the crystallisation of the crude dioxides crystallised from water in tufts of hair-like crystals or bunches of radiating prismatic needles and proved to be a *dihydrated hydrogen peroxide complex* of the β-dioxide (Found: C, 56·4, 56·7; H, 6·5, 6·7; N, 8·0. $C_{16}H_{24}O_6N_2$ requires C, 56·5; H, 7·1; N, 8·2%. A tetrahydrate of the β-dioxide would require C, 56·4; H, 7·7; N, 8·2%). This substance is many times as soluble in water as the α-isomeride. 95·6% Alcohol at 25° dissolves 1·16 wt.-% of it. It explodes at 210° (corr.) and remains unchanged when kept *in vacuo* over phosphoric anhydride.

The presence of molecular hydrogen peroxide in this compound was confirmed by direct tests. The material available being insufficient for repeated precise reductometric analysis by our usual procedure, two experiments were made as follows. (*a*) 10 Mg. each of the α-dioxide dihydrate and the β-dioxide complex were separately distilled with aqueous 1% sulphuric acid. The distillate from the β-specimen gave a positive reaction for peroxide with iodide and starch whereas that from the α-dioxide did not. (*b*) 10 Mg. each of the α-dioxide dihydrate and of the β-dioxide complex were separately dissolved in aqueous sulphuric acid (5 ml. of 2N.) in a stream of nitrogen, and 1 ml. of 5% potassium iodide and 1 ml. of 1% starch solution added to each. The β-dioxide complex gave an instantaneous blue colour; the α-dioxide developed a blue colour when kept. Both were then very slowly titrated with N/10-thiosulphate. The α-dioxide required 1·40 ml., the β-dioxide complex 2·15 ml. of thiosulphate solution. The latter thus has a content of total peroxidic oxygen 50% higher than the former corresponding to the presence of one mol. of hydrogen peroxide in the latter.

The β-dioxide complex was reduced by zinc dust in acid solution to the parent diphenylpiperazine.

The following salts of the β-dioxide were prepared: the *dipicrate*, small yellow needles with a high double refraction and a straight extinction, which explode at 207° (corr.) (Found: C, 46·1; H, 3·4; N, 15·2. $C_{28}H_{24}O_{14}N_8$ requires C, 46·2; H, 3·3; N, 15·4%); the *dihydrochloride*, a white microcrystalline powder (Found: C, 55·4; H, 6·1; N, 7·7. $C_{16}H_{20}O_2N_2Cl_2$ requires C, 55·1; H, 5·8; N, 8·2%); the *dinitrate*, colourless thin plates, rhomb-shaped or elongated with oblique ends, having low double refraction and an oblique extinction, which explode at 224° (corr.) (Found: C, 48·2; H, 5·3. $C_{16}H_{20}O_8N_4$ requires C, 48·5; H, 5·1%). The β-dioxide also yields an aurichloride, a sulphate, and a perchlorate more soluble in alcohol than the α-salts.

KING'S COLLEGE, STRAND, W.C.2.
THE GOVERNMENT LABORATORY, W.C.2.

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50. *The Infra-red Spectra of Carcinogens. Part I. Derivatives of Stilbene.*

By H. W. THOMPSON, EVA E. VAGO, M. C. CORFIELD, and S. F. D. ORR.

A survey has been made of the vibrational spectra of some carcinogens. This paper describes results for derivatives of stilbene. The spectra provide data which may be useful for analytical work, and correlations have been drawn up between important spectral features and the individual molecular structures. By use of such correlations it may be possible to identify the type of substitution in aromatic rings existing in such compounds.

THE main purposes of this investigation were (*a*) to begin a comprehensive survey of the infra-red absorption spectra of complex molecules which are important in the field of cancer research, and (*b*) to correlate spectral features with molecular structure in related series of molecules in which structural alterations are known to affect carcinogenic activity (Haddow, *Brit. Med. Bull.*, 1947, **4**, 331; Haddow, Harris, Kon, and Roe, *Phil. Trans.*, 1948, **241**, 147). We were stimulated to carry out this programme by discussions with the staff of the Chester Beatty Research Institute, from whom we have obtained most of the compounds examined. The compilation of the spectra of these compounds may well form a valuable basis for analytical work, such as has been developed for urinary keto-steroids by Dobriner, Liebermann, Rhoads, Williams, and Barnes (*J. Biol. Chem.*, 1948, **172**, 247). As regards structural diagnosis, much is now known about the correlation of certain absorption bands with particular atomic groupings (Thompson, *J.*, 1948, 328; Williams, *Rev. Sci. Instr.*, 1948, **19**, 135), and as more reference data have accumulated it has been found that the characteristic vibration frequencies of some groups may be affected by special electronic influences introduced by neighbouring substituents or structural factors. This has been illustrated clearly by the work on the steroids already mentioned (Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024). The present paper summarises results for some derivatives of stilbene.

Experimental Method.

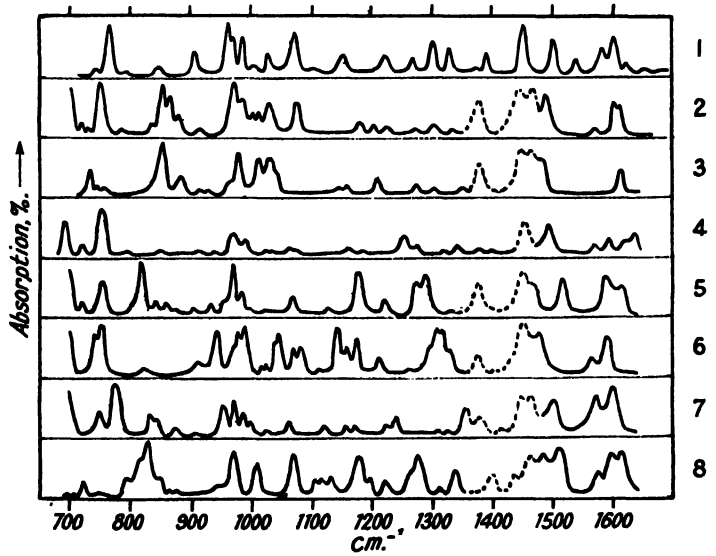
The spectra were measured between 5 and 15 μ. using the powdered solids ground to a paste with paraffin and pressed between rock-salt plates. Between 7 and 15 μ. a single-beam recording spectrometer was used with a rock-salt prism, and between 5 and 8 μ., where the absorption of atmospheric water vapour is strong, a double-beam recorder with a calcium fluoride prism was used. A few of the spectra were measured on a Perkin Elmer 12 C instrument with a rock-salt prism. The effective slit widths were about 5 cm.$^{-1}$ over the whole range. Unfortunately in the region 6·5—7·5 μ. there are paraffin absorption bands, and also, when the paste is used, scattering errors lead to inexact balancing of the double-beam recorder. For this reason some of the curves recorded over this range are uncertain, but no bands of major interest are to be expected here.

Results and Discussion.

The spectra are shown in Figs. 1—4. An experimental result of general interest was that with some of these compounds the Christiansen effect was observed as described recently for other slurries by Price and Tetlow (*J. Chem. Phys.*, 1948, **16**, 1157). This was clearly detectable by the very rapid changes of transmission coefficient near certain absorption bands. It may be significant that, in most cases of 4-dimethylaminostilbenes where it occurred, the phenomenon was particularly marked at about 1190 cm.$^{-1}$ (8·4 μ.), but several absorption bands in the same spectrum were usually affected.

FIG. 1.

Stilbene and derivatives.

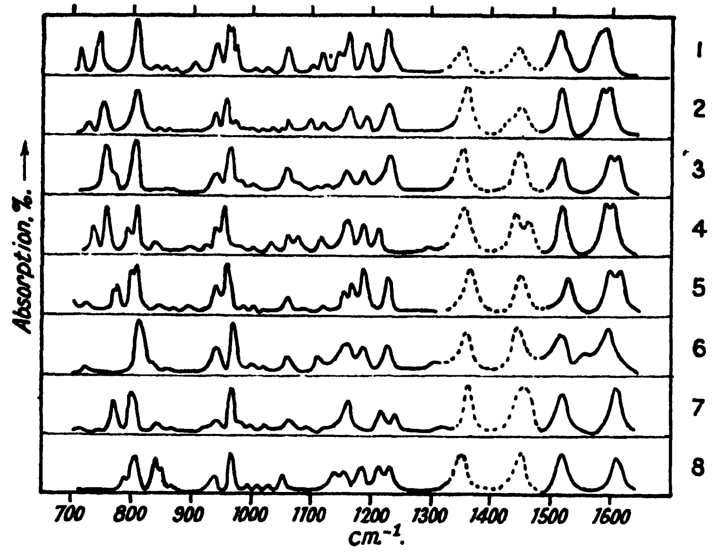


(1) *Stilbene.* (2) 2 : 4 : 6-*Trimethylstilbene.* (3) 2 : 4 : 6 : 2′ : 4′ : 6′-*Hexamethylstilbene.* (4) 2-*Aminostilbene.* (5) 4-*Aminostilbene.* (6) 2-*Dimethylaminostilbene.* (7) 3-*Dimethylaminostilbene.* (8) 4′-*Bromo*-4-*dimethylaminostilbene.*

The spectra shown in the figures reveal differences between the isomeric compounds and between related homologues which may be useful for analytical work.

FIG. 2.

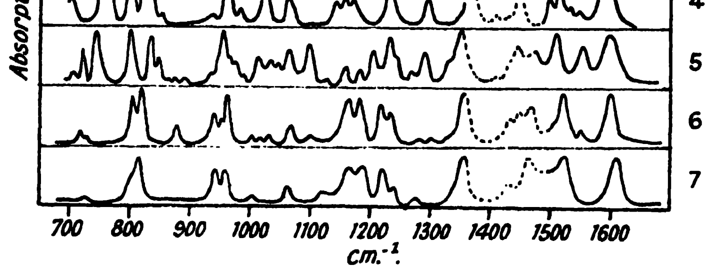
Stilbene derivatives.



(1) *4-Dimethylaminostilbene.* (2) *4-Dimethylamino-2′-methylstilbene.* (3) *4-Dimethylamino-2′-ethylstilbene.* (4) *4-Dimethylamino-2′-isopropylstilbene.* (5) *4-Dimethylamino-3′-methylstilbene.* (6) *4-Dimethylamino-4′-methylstilbene.* (7) *4-Dimethylamino-2′ : 6′-dimethylstilbene.* (8) *4-Dimethylamino-2′ : 4′ : 6′-trimethylstilbene.*

FIG. 3.

Stilbene derivatives.

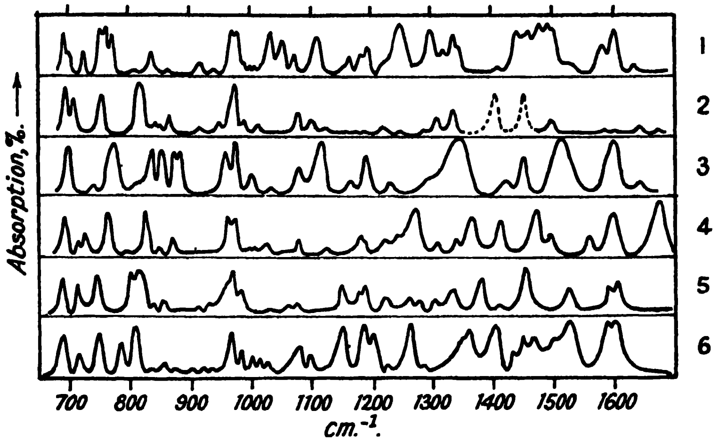


(1) *4′-Chloro-4-dimethylaminostilbene.* (2) *3′-Bromo-4-dimethylaminostilbene.* (3) *2′-Chloro-4-dimethylaminostilbene.* (4) *2-Chloro-4-dimethylaminostilbene.* (5) *4-Dimethylamino-2 : 2′-dimethylstilbene.* (6) *4-Dimethylamino-2′ : 4′-dimethylstilbene.* (7) *4 : 4′-Bisdimethylaminostilbene.*

Characteristic spectral features are to be expected of (*a*) the substituted aromatic nuclei, and (*b*) the $-CH=CH-$ group. Of the former, perhaps the most striking is that which originates in the deformation of residual C–H bonds out of the plane of the substituted aromatic ring to which they are attached (Whiffen and Thompson, *J.*, 1945, 268; Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246; Bell, Thompson, and Vago, *Proc. Roy. Soc.*, 1948, *A*, **192**,

FIG. 4.

Stilbene derivatives.



(1) 2-*Methoxystilbene.* (2) 4-*Bromostilbene.* (3) 4-*Nitrostilbene.* (4) 4-*Acetylstilbene.* (5) 4-*Ethylaminostilbene.* (6) 4-*Diethylaminostilbene.*

TABLE I.

Characteristic vibration frequencies of different types of substituted stilbene derivatives.

	Type of substitution,						
		di.			tri.		tetra.
Stilbene derivative.	Mono.	*o.*	*m.*	*p.*	1 : 2 : 3.	1 : 2 : 4.	1 : 2 : 3 : 5.
2 : 4 : 6-Trimethyl	750	—	—	—	—	—	852
2 : 4 : 6 : 2′ : 4′ : 6′-Hexamethyl	—	—	—	—	—	—	851
2-Amino	752	752	—	—	—	—	—
4-Amino	750	—	—	818	—	—	—
2-Dimethylamino	740	752	—	—	—	—	—
3-Dimethylamino	750	—	775	—	—	—	—
4-Dimethylamino	747	—	—	810	—	—	—
4-Dimethylamino-2′-methyl	—	752	—	809	—	—	—
4-Dimethylamino-2′-ethyl	—	757	—	809	—	—	—
4-Dimethylamino-2′-*iso*propyl	—	757	—	809	—	—	—
4-Dimethylamino-3′-methyl	—	—	778	810	—	—	—
4-Dimethylamino-4′-methyl	—	—	—	816	—	—	—
4-Dimethylamino-2′ : 6′-dimethyl	—	—	—	805	772	—	—
4-Dimethylamino-2′ : 4′ : 6′-trimethyl	—	—	—	807	—	—	845
4′-Chloro-4-dimethylamino	—	—	—	822	—	—	—
3′-Bromo-4-dimethylamino	—	—	772	812	—	—	—
2′-Chloro-4-dimethylamino	—	755	—	809	—	—	—
2-Chloro-4-dimethylamino	755	—	—	—	—	802	—
4-Dimethylamino-2 : 2′-dimethyl	—	746	—	—	—	803	—
4-Dimethylamino-2′ : 4′-dimethyl	—	—	—	821	—	807	—
4 : 4′-Bisdimethylamino	—	—	—	816	—	—	—
2-Methoxy	755	755	—	—	—	—	—
4-Bromo	750	—	—	814	—	—	—
4′-Bromo-4-amino	—	—	—	830	—	—	—
4-Nitro	766	—	—	835	—	—	—
4-Acetyl	762	—	—	824	—	—	—
4-Ethylamino	750	—	—	810	—	—	—
4-Diethylamino	750	—	—	812	—	—	—

498). Intense bands occur in the region 700—900 cm.$^{-1}$ according to the number and position of substituents in the aromatic nucleus. Two other vibrations of the aromatic nucleus near 1500 cm.$^{-1}$ and 1600 cm.$^{-1}$ frequently occur, but their intensities, both absolute and relative to each other, are variable. The C–H out-of-plane vibrations in the present series of compounds fall into line well with the earlier deductions. Table I summarises the data, from which it is seen that with few exceptions the different substitution types have vibration frequencies lying close to fixed values, *e.g.*, *ortho*-derivatives near 755 cm.$^{-1}$, *meta* near 775 cm.$^{-1}$, *para* from 805 to 820 cm.$^{-1}$, 1 : 2 : 4-trisubstituted derivatives near 805 cm.$^{-1}$, and 1 : 2 : 3 : 5-

tetrasubstituted derivatives near 850 cm.$^{-1}$. The conjugation of highly polar groups such as NO_2 or $CO{\cdot}CH_3$, causes some displacement of frequencies, but this occurs also in simpler compounds when such groups are attached to single benzene nuclei. It therefore seems possible to use such correlation rules for diagnostic purposes with the stilbene derivatives. A further refinement may be added. The results of Table I suggest that an ambiguity may arise between monosubstituted and *ortho*-disubstituted rings, both having the strong band near 750 cm.$^{-1}$. It was found, however, by Whiffen (Thesis, Oxford, 1946) that a large variety of monosubstituted benzene derivatives have a strong band at 690—700 cm.$^{-1}$, whilst the *ortho*-disubstituted derivatives have no such band. This band, occurs similarly with monosubstituted rings in the stilbenes, but not with *ortho*-disubstituted rings. A similar band occurs with *meta*-disubstituted rings near 700 cm.$^{-1}$, but any ambiguity between monosubstituted and *meta*-disubstituted rings will as a rule be removed by consideration of their bands near 750 and 775 cm.$^{-1}$, respectively.

The spectra of olefins containing the $-CH{=}CH-$ group show a strong band near 965 cm.$^{-1}$ which arises from a vibration involving deformation of the C–H bonds. This occurs with all the stilbenes measured, although it is slightly displaced in the different cases. Any alteration in the electronic structure of this group caused by substituents in the phenyl nuclei might be expected to modify the frequency; alternatively, large groups in the *ortho*-positions might so affect the structure as to influence its vibration. There is some indication that the presence of blocking-groups in the *ortho*-positions raises the frequency, but it cannot be regarded as definite.

One question upon which the present results give no guide is the coplanarity or otherwise of the two phenyl nuclei. The possible connexion between this and carcinogenic activity has been discussed by Haddow, Harris, Kon, and Roe (*loc. cit.*). It seems possible that, by use of the rules given above for the identification of particular nuclei substituted in different ways, the study of single crystals with polarised radiation and the reflecting microscope (Barer, Cole, and Thompson, *Nature*, 1949, **163**, 198) may throw further light on this.

Another general matter is being examined, namely, the effect of the state of aggregation on the spectra. There are signs of small shifts in the positions of some bands on changing from solids to solutions, and this may to some extent affect the application of structural diagnosis.

We are most grateful to Prof. G. A. R. Kon, F.R.S., for the specimens of aminostilbenes examined.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, June 30th*, 1949.]

51. *The Infra-red Spectra of Carcinogens. Part II. Polynuclear Hydrocarbons.*

By S. F. D. ORR and H. W. THOMPSON.

Vibration spectra of some polynuclear aromatic hydrocarbons, which are of interest in cancer research, have been measured. Attempts have been made to correlate spectral features with molecular structure, particularly with regard to the vibrations of C—H bonds in substituted aromatic rings.

IN continuation of work described in the preceding paper, we now give results for the spectra of some polynuclear hydrocarbons and a few related molecules. As before, the data may be useful for analytical work, and as regards the correlation of spectrum with molecular structure it was interesting to discover how far the rules given in the previous paper for the identification of aromatic nuclei substituted in different positions are applicable when the substituent bonds are themselves part of other rings of the ring-system.

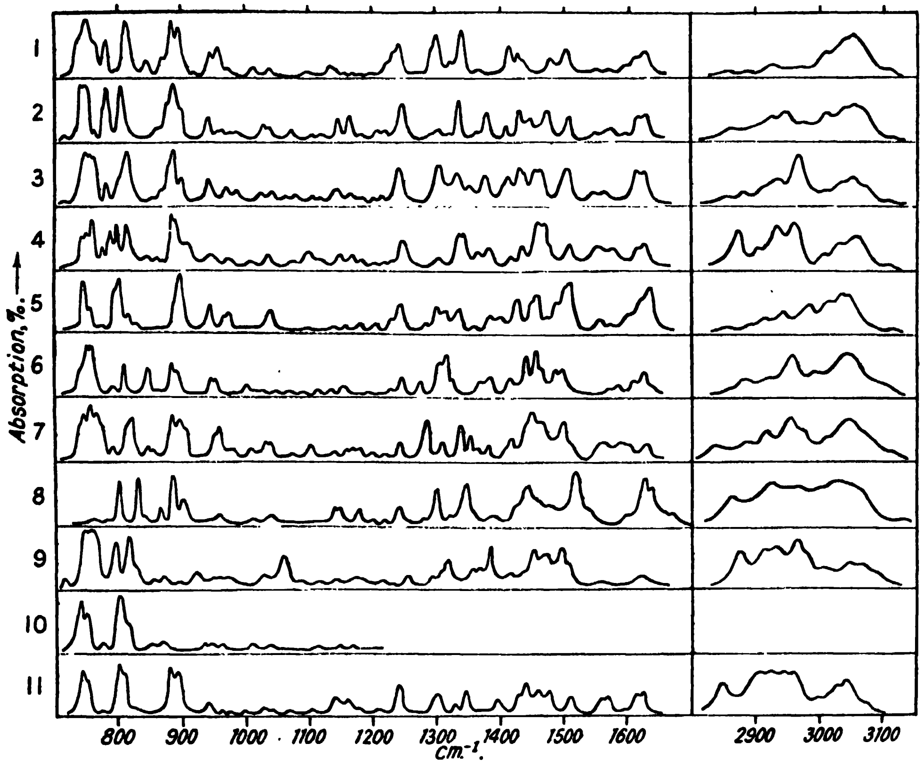
The experimental methods were as described in the preceding paper, except that most of the spectra were measured on a Perkin Elmer 12 C spectrometer, with a prism of rock salt or lithium fluoride. The compounds were measured as thin solid films made by melting a small sample and pressing it between rock-salt plates. In the case of 9 : 10-dihydroanthracene, which tends to decompose on melting, a paste in paraffin was used.

The spectra are shown in Figs. 1, 2, and 3. The broad features of the spectra of the 1 : 2-benzanthracenes (Fig. 1) are a number of strong bands between 700 and 900 cm.$^{-1}$, a region of comparative transparency at 900—1200 cm.$^{-1}$, and a complex arrangement of bands between 1200 and 1700 cm.$^{-1}$. The vibrations giving rise to the intense bands at 700—900 cm.$^{-1}$ will include the out-of-plane deformations of C—H bonds in the substituted aromatic rings. It is clear that in the present set of compounds the situation is more complex than with the stilbenes described in the preceding paper, but several points emerge.

All the compounds in Fig. 1, except 2′ : 6-dimethyl-1 : 2-benzanthracene, contain an aromatic ring which is 1 : 2-disubstituted only. It is therefore noticeable that all except this compound have a strong band around 750 cm.$^{-1}$, in the characteristic position for an *ortho*-disubstituted ring, although the small shift from one molecule to another is rather bigger than usual. This rule for 1 : 2-disubstitution also appears to hold for the other compounds in Figs. 2 and 3, except 9 : 10-dihydroanthracene and anthracene itself, but in many cases there is a shift of 10 cm.$^{-1}$ to higher or lower frequencies.

FIG. 1.

1 : 2-*Benzanthracenes.*



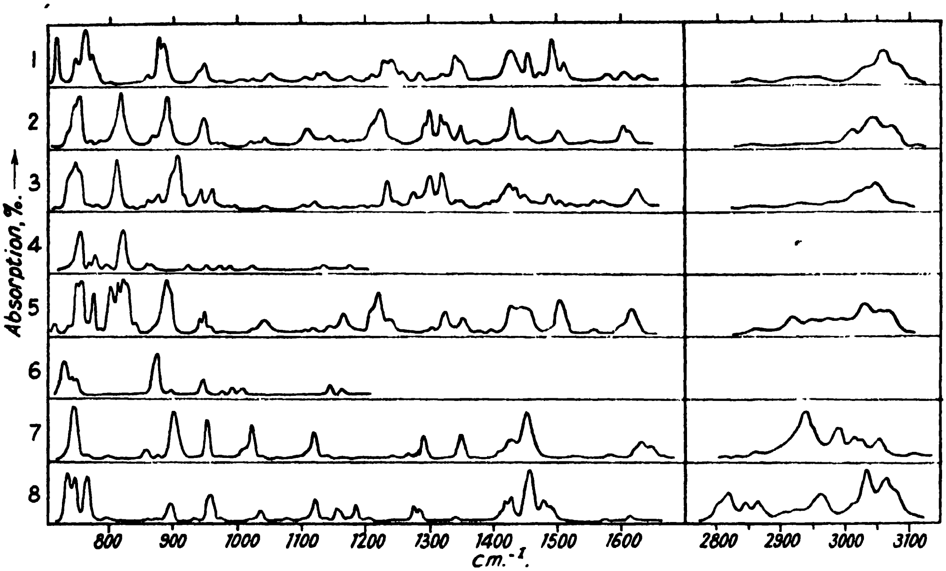
(1) 1 : 2-*Benzanthracene.* (2) 5-*Methyl*-1 : 2-*benzanthracene.* (3) 5-*Ethyl*-1 : 2-*benzanthracene.* (4) 5-n-*Propyl*-1 : 2-*benzanthracene.* (5) 7-*Methyl*-1 : 2-*benzanthracene.* (6) 9-*Methyl*-1 : 2-*benzanthracene.* (7) 1′-*Methyl*-1 : 2-*benzanthracene.* (8) 2′ : 6-*Dimethyl*-1 : 2-*benzanthracene.* (9) 9 : 10-*Dimethyl*-1 : 2-*benzanthracene.* (10) 6 : 9 : 10-*Trimethyl*-1 : 2-*benzanthracene.* (11) 5 : 6-cyclo*Penteno*-1 : 2-*benzanthracene.*

Another noticeable characteristic of the benzanthracenes (Fig. 1) is a strong band near 890 cm.$^{-1}$, which occurs in all cases unless there is substitution also in the 9 : 10-positions. This suggests that the central ring can be regarded as being substituted in the 1 : 2 : 4 : 5-positions. For ordinary 1 : 2 : 4 : 5-tetrasubstituted benzene derivatives, a band has previously been found at about 875 cm.$^{-1}$. It should be noted however that 9-methyl-1 : 2-benzanthracene has a weaker band at 890 cm.$^{-1}$. Among the other compounds of Figs. 2 and 3 with one exception all those with an unsubstituted middle anthracene ring show the band near 890 cm.$^{-1}$, and with one exception it is absent from molecules with essentially different structures, such as a reduced middle anthracene ring. The exception is again 9 : 10-dihydroanthracene, which shows a band near 890 cm.$^{-1}$, although this is weaker than usual.

The other strong bands between 700 and 900 cm.$^{-1}$ are more difficult to correlate. One possible regularity is suggested by the strong bands at 800—810 cm.$^{-1}$ found in all compounds (except acridine derivatives) containing 1 : 2 : 3 : 4-substitution. Although simple 1 : 2 : 3 : 4-tetrasubstituted benzene derivatives have not been available to enable us to determine the

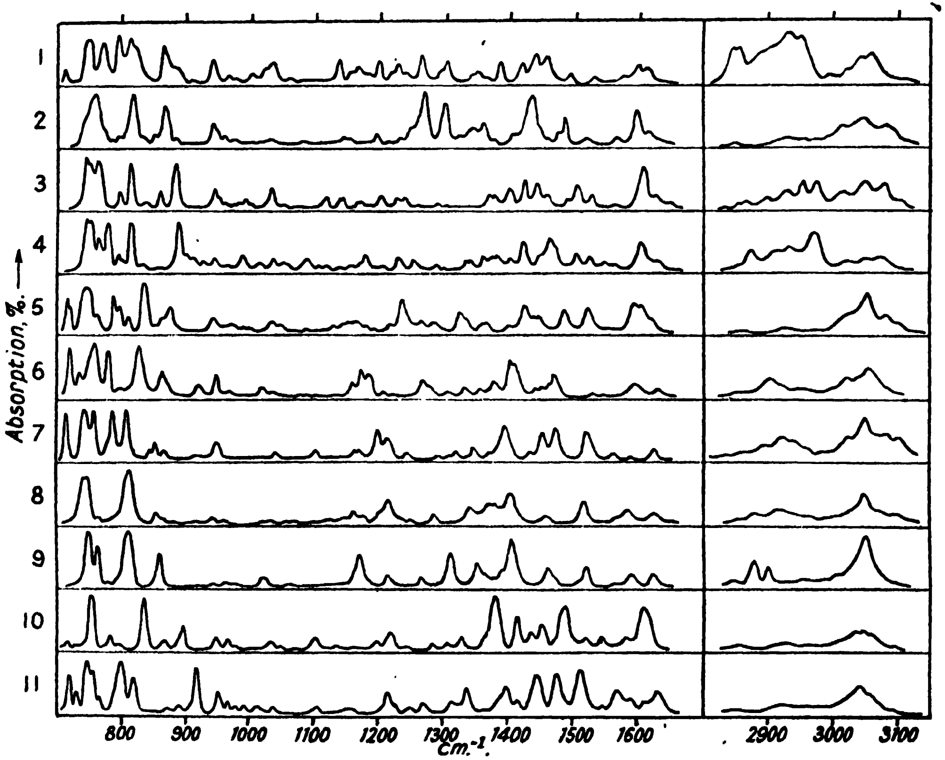
FIG. 2.

Dibenzanthracenes and anthracenes.



(1) 1 : 2-3 : 4-*Dibenzanthracene*. (2) 1 : 2-5 : 6-*Dibenzanthracene*. (3) 1 : 2-6 : 7-*Dibenzanthracene*. (4) 9 : 10-*Dihydro*-1 : 2-5 : 6-*dibenzanthracene*. (5) 3′-*Methyl*-1 : 2-5 : 6-*dibenzanthracene*. (6) *Anthracene*. (7) 2 : 3-*Dimethylanthracene*. (8) 9 : 10-*Dihydroanthracene*.

FIG. 3.



(1) 1 : 2-cyclo*Pentenophenanthrene*. (2) *Chrysene*. (3) 2-*Methyl*-3 : 4-*benzphenanthrene*. (4) 2-iso*Propyl*-3 : 4-*benzphenanthrene*. (5) 1 : 2-5 : 6-*Dibenzphenanthrene*. (6) 1 : 2-*Benzfluorene*. (7) 3 : 4-*Benzfluorene*. (8) 1 : 2-5 : 6-*Dibenzfluorene*. (9) 1 : 2-7 : 8-*Dibenzfluorene*. (10) 3 : 4-6 : 7-*Dibenzacridine*. (11) 1 : 2-8 : 9-*Dibenzacridine*.

characteristic C—H out-of-plane frequency in this type, we might argue by extrapolation from the results with the other compounds that it would have a value close to that just found.

A less prominent band which seems to persist throughout the 1 : 2-benzanthracenes lies near 1240 cm.$^{-1}$, although here a few small deviations occur which, taken with the weaker nature of the band, obscure the position.

In the region 2800—3100 cm.$^{-1}$ these compounds have bands due to the C—H stretching vibrations. Beyond the general and expected result that the aromatic C—H vibrations give bands at 3000—3100 cm.$^{-1}$ and the aliphatic C—H vibrations at lower frequencies, 2850—2950 cm.$^{-1}$, no very significant conclusions can at present be drawn.

We are again indebted to Prof. G. A. R. Kon, F.R.S., for most of the pure hydrocarbon examined.

The Physical Chemistry Laboratory, Oxford. [*Received, June 30th*, 1949.]

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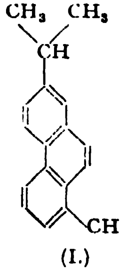
52. *Infra-red Studies of Retene and its Hydrogenation Products.*

By P. V. Laakso, S. F. D. Orr, and H. W. Thompson.

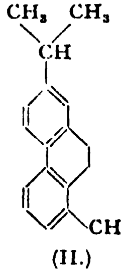
The infra-red absorption spectra of retene, dihydroretene, octahydroretene, and perhydroretene have been measured, between 3 and 15 μ. They have been used to provide analytical methods of studying the nature of the products formed in the hydrogenation of retene by different methods. It has been found that these products are confined to dihydro-, octahydro- and perhydro-retene, and this corresponds to the stability of these compounds in which only aromatic and fully saturated rings occur. Similar reactions involving the catalytic dehydrogenation of hydroretenes have been examined. A melting-point diagram is given for retene and dihydroretene, which form a complete series of mixed crystals.

The presence of the phenanthrene nucleus in such important classes of compound as the sterols, bile acids, and certain alkaloids has prompted further work on naturally occurring polynuclear aromatic compounds and their derivatives.

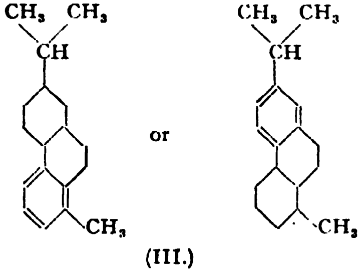
Retene [1-methyl-7-*iso*propylphenanthrene (I)] is of particular interest in relation to the resin acids and the diterpenes. It can theoretically form seven hydroretenes, in which 2, 4, 6, 8, 10, 12, and 14 hydrogen atoms respectively have been added to the molecule. Retene and perhydroretene can each exist in only one form, but all the others are capable of structural isomerism. For example, there are theoretically 16 isomers of dihydroretene, depending on which bond has been saturated, and with the more fully hydrogenated derivatives the number of isomers is still greater. On theoretical grounds, the isomers may differ greatly in stability, and in practice dihydroretene is found only as the 9 : 10-compound (II), formed from retene either by catalytic reduction or by the action of sodium and amyl alcohol. On grounds of ring strain, the most stable derivatives would be expected to be dihydroretene, octahydroretene (III), and perhydroretene (IV). These derivatives should be formed preferentially in the catalytic reduction of retene. It has been shown, for example, that reduction of retene in presence of a nickel catalyst gives perhydroretene (Ipatiev, *Ber.*, 1909, **42**, 2095; Laakso, *Ann. Acad. Sci. Fennicæ*, 1949, *A*, No. 28), whilst if copper chromite is used a mixture of dihydroretene and octahydroretene is formed (Laakso, *loc. cit.*). Whenever the hydrogenation with a nickel catalyst is interrupted before the full complement of hydrogen has been taken up, a mixture of these particular hydroretenes and retene is obtained. Thus, if the equivalent of four hydrogen atoms has been absorbed, no tetrahydroretene is found but only retene and perhydroretene.



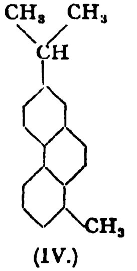
(I.)



(II.)



(III.)



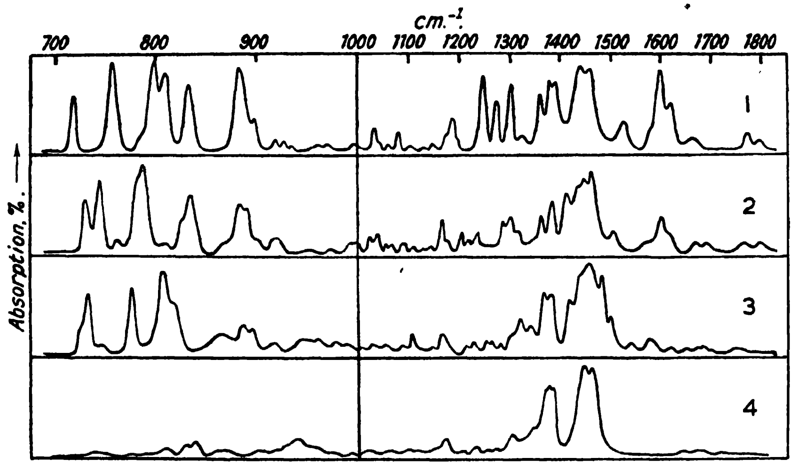
(IV.)

However, Bamberger and Lodter (*Ber.*, 1887, **20**, 3073) claimed to have prepared tetrahydroretene using sodium and amyl alcohol. Liebermann and Spiegel (*Ber.*, 1889, **22**, 779) similarly claimed to have prepared dodecahydroretene using phosphorus and hydrogen iodide, and Virtanen a whole series of hydroretenes by the same methods (*Ber.*, 1920, **53**, 1880). In these investigtions no chemical tests were given which characterised the products, which might have been mixtures. It therefore seemed appropriate to apply infra-red absorption spectroscopy to the problem, and the results have indeed substantiated the argument outlined above about the relative stability of the hydroretenes. Some analogous problems involved in the dehydrogenation of hydroretene have been examined by the same method.

The spectrometers used were automatic recorders, described in detail elsewhere (Thompson and Whiffen, *J.*, 1945, 269; Richards and Thompson, this vol., p. 124). A rock-salt prism was used for most of the work, but the region 2—7 μ. was also measured with prisms of calcium fluoride and lithium fluoride. The compounds were measured as thin solid layers melted on rock-salt plates, as liquids, or in dilute solutions in carbon tetrachloride or bromoform as indicated below.

The Hydrogenation of Retene.—The spectra of pure samples of retene, dihydroretene, octahydroretene, and perhydroretene were first determined for reference. These are shown in Figs. 1 and 2.

Fig. 1.



(1) *Retene, solid film.* (2) *Dihydroretene, solid film.* (3) *Octahydroretene, liquid.* (4) *Perhydroretene, liquid.*

Part of the spectrum of retene was previously recorded by Barnes, Gore, Liddel, and Williams (*Ind. Eng. Chem. Anal.*, 1943, **15**, 659). It is seen that well-marked differences exist between the spectra in several spectral regions, which serve to characterise the compounds, and it seems certain that other hydroretenes would have equally distinctive features.

Attempts were then made to prepare tetrahydro-, hexahydro-, octahydro-, and decahydroretene by the methods described by Virtanen. For tetrahydro-retene, retene was reduced by sodium in amyl alcohol in several ways, namely, (*a*) with a small amount of sodium and heating with an open flame, (*b*) with a larger amount of sodium and similar heating, (*c*) with a further excess of sodium, and (*d*) with an excess of sodium but heating in an oil-bath. The spectra of the products, and of distillation fractions from each of them, were then measured. In the first three cases, a moderately strong band, the originator of which appeared to become concentrated in the higher-boiling fractions, occurred at 1740 cm.$^{-1}$ and was attributed to a carbonyl group. This did not occur with material obtained by method (*d*) in which local over-heating was avoided, and the compound responsible for it, which could not have been present in great amount, can be confidently regarded as a by-product formed from amyl alcohol. All the other bands in the spectra could be satisfactorily accounted for as a mixture of two or more of those of retene, dihydroretene, and octahydroretene.

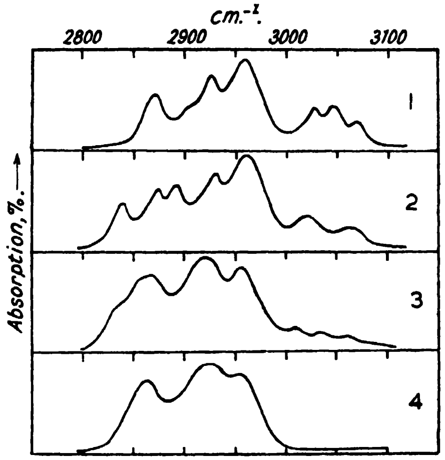
The more saturated hydroretenes were made by reduction of retene with phosphorus and hydrogen iodide. In this case all the bands found in the spectra of the products were explicable in terms of retene, dihydroretene, octahydroretene, and perhydroretene. As the proportion of hydrogen taken up is increased, the more fully hydrogenated derivatives become more prominent, as might be expected.

It was found that the boiling point of the mixture of hydrogenation products did not vary gradually and continuously during a distillation, and this suggested the formation of azeotropic mixtures. It will be shown later that retene and dihydroretene form a complete series of mixed crystals.

Dehydrogenation of Hydroretenes.—When a sample of dihydroretene, which had been prepared by catalytic reduction of retene and purified by recrystallisation, was dehydrogenated with Raney nickel, it did not evolve the full equivalent of hydrogen, but about 10% less (Laakso, *Ann. Acad. Sci. Fennicæ*, 1949, *A*, No. 32). It had been suggested that this result might have arisen by disproportionation. The spectral examination of the sample of dihydroretene showed however that it contained a small amount of retene. By repeated recrystallisation, it was possible to prepare a specimen of dihydroretene, m. p. 56—58°, the spectrum of which was free from the bands of retene. Dihydroretene was found to become concentrated in the mother-liquor rather than in the crystals, and the purest specimen was found in the last mother-liquor after fractional evaporation and filtration of the alcoholic solution. Retene and dihydroretene appear to form a complete series of mixed crystals, the melting point increasing as the percentage of retene increases (Fig. 3). The presence of retene in the sample of dihydroretene would account for the deficit of hydrogen in the dehydrogenation discussed above. Indeed, the gradual melting over 2° of the sample of dihydroretene thought to be pure suggests that about 1% of impurity may still be present, but the spectra show definitely that this impurity cannot be retene.

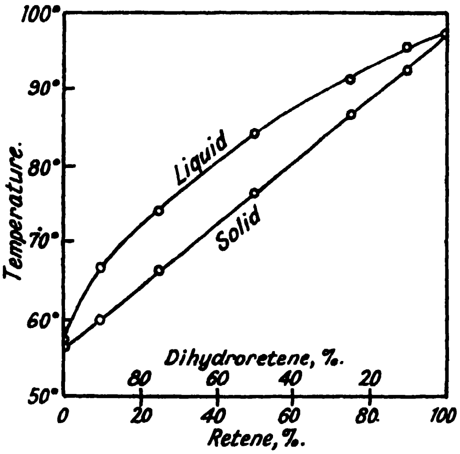
FIG. 2.

Solutions in carbon tetrachloride.



(1) *Retene*, 2%. (2) *Dihydroretene*, 2%.
(3) *Octahydroretene*, 2%.
(4) *Perhydroretene*, 1%.

FIG. 3.



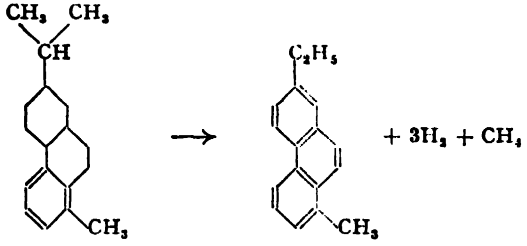
Simultaneously with the liberation of hydrogen in the dehydrogenation process, methane is formed. This presumably comes from a degradation of the *iso*propyl group, but spectral changes which might confirm this would be slight and have not been detected.

The dehydrogenation of octahydroretene has also been studied. With Raney nickel at 220° a smooth reaction occurs in which hydrogen is liberated, but in smaller amount than would be required for complete dehydrogenation. At the same time much methane is formed. These results can be explained by the occurrence of two reactions simultaneously with the straight dehydrogenation.

In the first, disproportionation leads to retene and perhydroretene:

$$2C_{18}H_{26} \longrightarrow C_{18}H_{18} + C_{18}H_{32} + H_2$$

and in the second, the *iso*propyl radical loses methane, subsequent dehydrogenation leading to 1-methyl-7-ethylphenanthrene :



The product obtained from the dehydrogenation of octahydroretene was found spectroscopically to show bands of retene and perhydroretene, and also other unexplained bands. The sample was then separated into a crystalline and an oily fraction. The former was almost pure retene; the latter contained much perhydroretene and also the unidentified component. Although the third component could not be completely identified from its spectral features, there is no doubt that it contains aromatic nuclei and methyl groups. It has not yet been possible to obtain a synthetic sample of 1-methyl-7-ethylphenanthrene to establish the expected identity.

EXPERIMENTAL.

Retene.—The retene used in these experiments was prepared, from the higher fractions of tar, by distillation and fractional distillation (Talvitie and Laakso, *Ann. Acad. Sci. Fennicæ*, 1946, *A*, No. 21, 10). The m. p. of the pure sample was 98—98·5°.

Dihydroretene.—The dihydro-compound was prepared by the reduction of retene with sodium in amyl alcohol (Virtanen, *loc. cit.*). The infra-red spectrum showed that the product still contained retene, but a retene-free sample, m. p. 56—58°, was isolated from the mother-liquor. A better method for the preparation of pure dihydroretene is to use more sodium, under slightly modified conditions.

10 G. of retene were dissolved in 100 c.c. of dry amyl alcohol and heated in an oil-bath at 130°. 8 G. of sodium were added during 2 hours. When all the sodium had dissolved the reaction mixture was poured into water, and the amyl alcohol layer separated and washed with water until it was neutral. Amyl alcohol was distilled off in steam, and the residual mixture of hydroretenes kept at $-10°$ overnight. The crystals formed were filtered off and recrystallised twice from alcohol. The resultant dihydro-compound had m. p. 56—58°, and was shown by its infra-red spectrum to contain no trace of retene.

Octahydroretene.—This was prepared by catalytic reduction of retene with a copper chromite catalyst (Laakso, *Ann. Acad. Sci. Fennicæ*, 1949, *A*, No. 28). It was a pale yellow, very viscous oil, b. p. 191—192°/1·0 mm.

Perhydroretene.—This hydrocarbon was prepared by the catalytic reduction of retene with a nickel–kieselguhr catalyst (Laakso, *loc. cit.*). It was a colourless, not very viscous, oil, b. p. 332—335°/760 mm.

Preparation of " Tetrahydroretene."—(a) *With direct heating.* A solution of 10 g. of retene in 75 c.c. of amyl alcohol was heated to boiling on a wire-gauze, and 9 g. of sodium, cut into small pieces, were added during 2 hours. The mixture was poured into water, the amyl alcohol layer was separated, the solvents were removed by distillation, and " tetrahydroretene " was isolated as described by Virtanen, as a yellowish viscous oil, b. p. 180—183°/10 mm.

(b) *With excess of sodium and direct heating.* 10 G. of retene in 400 c.c. of amyl alcohol were heated to boiling on a wire-gauze. 25 G. of sodium, cut in small pieces, were added during 3 hours. Subsequent treatment was as in (a) above, three different fractions being collected during distillation under reduced pressure.

(c) *With excess of sodium and indirect heating.* The procedure was the same as in (b), but the flask was placed in an oil-bath heated to 130°. The product was distilled *in vacuo* three times, and two main fractions were taken. The first fraction (2·5 g.), b. p. 190—195°/1·0 mm., a yellow, viscous oil, was pure octahydroretene (Found : C, 89·5; H, 10·6. Calc. for $C_{18}H_{26}$: C, 89·2; H, 10·8%). The second fraction (3·0 g.), b. p. 220—223°/10 mm., a yellow viscous oil, gave analytical data corresponding to tetrahydroretene (Found : C, 90·5; H, 9·3. Calc. for $C_{18}H_{22}$: C, 90·7; H, 9·3%).

Reduction of Octahydroretene with Sodium.—5 G. of octahydroretene were dissolved in 100 c.c. of amyl alcohol and heated at 130° in an oil-bath. 10 G. of sodium, in small lumps, were added during 2 hours. Subsequent treatment, as in (a) above, gave 4 g. of a product, b. p. 190—195°/1·0 mm., which was a viscous, yellow oil, identical with the original sample of octahydroretene.

Preparation of " Hexahydroretene."—6 G. of retene, 7 g. of hydrogen iodide, and 3 g. of red phosphorus were heated in an atmosphere of carbon dioxide, in a sealed tube, so that the temperature rose to 200° during 3 hours. The tube was maintained at this temperature for 10 hours as described by Virtanen (*loc. cit.*). The product was boiled with water and extracted with ether, the ethereal extract was washed with water and dried (Na_2SO_4), the ether was evaporated, and the residue was distilled *in vacuo*. The fraction, b. p. 175—177°/10 mm., was collected, and its analysis found to correspond to that for " hexahydroretene " (Found : C, 90·1; H, 10·2. Calc. for $C_{18}H_{24}$: C, 89·9; H, 10·1%).

Preparation of Octahydroretene.—The procedure was the same as above, but the temperature was raised to 240° during 4 hours and was maintained at that level for 10 hours. The fraction, b. p.

163—165°/10 mm., was collected: its analysis corresponded to that of octahydroretene (Found: C, 89·1; H, 10·7. Calc. for $C_{18}H_{26}$: C, 89·2; H, 10·8%).

Preparation of Decahydroretene.—The procedure was again as above, but the temperature was raised to 285° during 4 hours and maintained for 10 hours. The fraction, b. p. 155—158°/750 mm., was collected and gave an analysis corresponding to decahydroretene (Found: C, 88·7; H, 11·2. Calc. for $C_{18}H_{28}$: C, 88·5; H, 11·5%).

Dehydrogenation of Dihydroretene.—1 G. of dihydroretene, m. p. 64—65°, and 0·3 g. of Raney nickel were heated, in a distillation flask connected to a gasometer, on an oil-bath at 220° until the evolution of gas had ceased. The dehydrogenation product was dissolved in ether and separated from the catalyst by filtration. It had m. p. 89—91°, raised by recrystallisation to 98—99°.

Dehydrogenation of Octahydroretene.—(a) *Incomplete dehydrogenation.* 1 G. of octahydroretene, b. p. 191—193/10 mm., and 0·3 g. of Raney nickel were similarly heated, until about 200 c.c. of gas had been evolved (corresponding to about 2 moles of hydrogen). The dehydrogenation product was dissolved in ether and separated from the catalyst by filtration.

(b) *Complete dehydrogenation.* 10 G. of octahydroretene, b. p. 191—193°/10 mm., and 3 g. of Raney nickel were similarly heated until the evolution of gas had ceased. The dehydrogenation product was separated from the catalyst by filtration when hot, and, on cooling, divided into a crystalline and an oily part. The crystals, m. p. 98—99°, were almost pure retene; the oily part was divided into two fractions of different boiling point and their infra-red spectra examined.

THE DYSON PERRINS LABORATORY AND THE
PHYSICAL CHEMISTRY LABORATORY, OXFORD.

[*Received, June 30th,* 1949.]

53. *Vibrational Spectra of Alkyl Esters of Phosphorus Oxy-acids.*

By C. I. MEYRICK and H. W. THOMPSON.

The infra-red and Raman spectra of some alkyl esters of phosphorus oxy-acids have been measured and correlated with the molecular structure. The dialkyl hydrogen phosphites show a band which indicates a P—H bond, and implies a structure $(RO)_2HPO$ for these compounds. Characteristic frequencies for the P=O and P—O links are also suggested, and other correlations are discussed. There is reason to suppose that the P—H bond can undergo hydrogen bridge formation with neighbouring oxygen atoms.

ALTHOUGH few previous studies of the vibrational spectra of the organic derivatives of phosphorus oxy-acids have been recorded, the subject is interesting in several connexions. First, it would be useful to know whether characteristic oscillation frequencies exist for the P=O and P—O linkages, and the measurement of band intensities in the infra-red and Raman spectra might provide information about the ionic character and polarisability of these bonds. Similar measurements have recently been made for silicon–oxygen bonds (Richards and Thompson, *J.*, 1949, 124) and for related structures such as the C=O linkage (Hartwell, Richards, and Thompson, *J.*, 1948, 1436). Secondly, the increasing application of infra-red measurements to biochemical problems, both for analysis and for structural diagnosis, makes it desirable to have spectra of relevant compounds containing phosphorus for reference purposes in connexion with possible studies of phosphate metabolism and general work of this kind. Thirdly, some questions about the structure of the phosphorus oxy-acids themselves may be elucidated from the vibrational spectra.

A survey has therefore been begun of the Raman and infra-red spectra of a series of alkyl esters of phosphorus oxy-acids, and the present paper summarizes the results for several classes of compound. It will be found that useful conclusions can already be drawn with regard to some of the points indicated above.

EXPERIMENTAL METHOD.

The compounds whose spectra have been measured were synthetic products supplied by the Chemical Defence Experimental Establishment, Porton:

	n_D^{20}.	B. p.
Dimethyl hydrogen phosphite	1·4030	38°/2·5 mm.
Diethyl hydrogen phosphite	1·4080	77/17 mm.
Di*iso*propyl hydrogen phosphite	1·4080	41·5/0·5 mm.
Trimethyl phosphite	1·4088	86—86·5/351 mm.
Triethyl phosphite	1·4130	74/21 mm.
Dimethyl methylphosphonate	1·4148	79·7/20 mm.
Diethyl methylphosphonate	1·4140	56·5/3·5 mm.
Di*iso*propyl methylphosphonate	1·4109	50·5—51·5/1 mm.
Diethyl ethylphosphonate	1·4161	66—66·5/3 mm.
Di*iso*propyl ethylphosphonate	1·4151	38/0·09 mm.

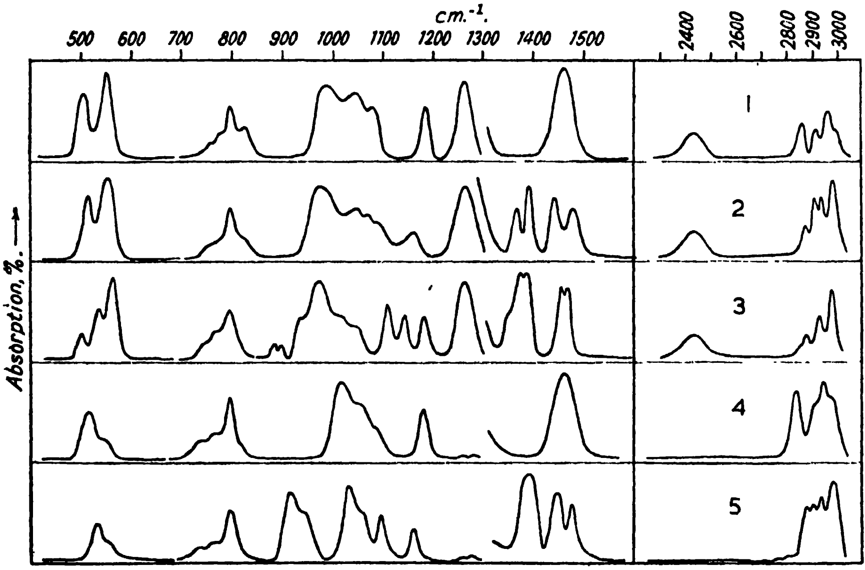
The infra-red spectra between 2 and 2·5μ. were measured with a Perkin Elmer 12 C recording spectrometer, with prisms of rock salt, potassium bromide, and lithium fluoride. Some spectra between 6 and 15μ. were also recorded on a single-beam spectrometer which has been described elsewhere (Whiffen and Thompson, *J.*, 1945, 268). Hitherto, thin films of the liquids have been used, pressed between a pair of rock salt or potassium bromide plates. Care was taken to minimise hydrolysis of the samples by damp air, and the measurements were made as rapidly as possible. As explained below, some measurements were repeated after the sample had been left in contact with damp air, and these served to indicate some of the spectral changes likely to occur in such circumstances.

The Raman spectra were measured photographically using a Hilger E518 instrument with glass prism, Ilford H.P. 3 plates being used. The exciting source was a 500-watt Hanovia cylindrical mercury arc, placed alongside a cylindrical glass tube containing a copper-ammonium salt solution. The latter acted both as a filter for the 4358A. line and as a condensing lens. The slight continuum was reduced by the introduction of further filters, a dilute solution of a rhodamine dye being sometimes used. Lines from a copper arc and neon discharge tube were used as reference standards.

Results.

The infra-red absorption spectra are shown in Figs. 1 and 2. The intensities for different compounds are not strictly comparable owing to the small differences in the thickness of the liquid used; and also different spectral regions for a given compound were measured with different thicknesses of material in order to bring up weak bands. This does not, however, affect the main conclusions of the present work. For later quantitative measurements on the intensities of the bands, it will be necessary to use known concentrations in a solvent, or alternatively known pressures of the vapours. It may be noted that the bands between 1300 and 1550 cm.$^{-1}$ are usually much weaker than many others in the spectra.

Fig. 1.

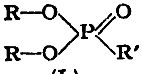


(1) *Dimethyl hydrogen phosphite.* (2) *Diethyl hydrogen phosphite.* (3) *Diisopropyl hydrogen phosphite.* (4) *Trimethyl phosphite.* (5) *Triethyl phosphite.*

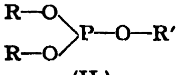
The Raman data and the position of the infra-red absorption bands are summarised in Table I and II.

Discussion.

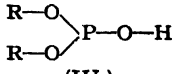
A number of interesting deductions can be made from these results. For example, in both the infra-red and the Raman spectra, the dialkyl hydrogen phosphites show a band near 2435 cm.$^{-1}$ which is absent from the spectra of all other compounds. There can be no doubt that this is due to a stretching vibration of the P—H link, corresponding to that of Si—H bonds near 2200 cm.$^{-1}$. In phosphine there is a P—H stretching vibration frequency at 2327 cm.$^{-1}$. Now the phosphonates have formula (I), and the trialkyl phosphites (II). For the dialkyl hydrogen phosphites two possibilities arise, namely (III) and (IV), and the spectra therefore indicate (IV), at any rate for the compounds measured. It is possible, however, that when the radicals R are changed this conclusion may not apply.



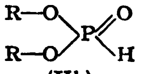
(I.)



(II.)

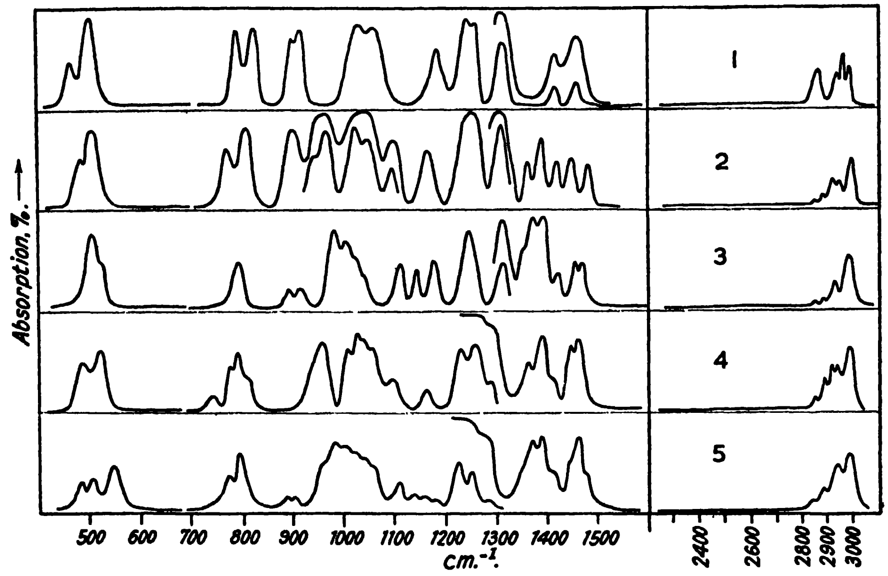


(III.)



(IV.)

FIG. 2.



(1) *Dimethyl methylphosphonate.* (2) *Diethyl methylphosphonate.* (3) *Diisopropyl methylphosphonate.* (4) *Diethyl ethylphosphonate.* (5) *Diisopropyl ethylphosphonate.*

TABLE I.

Phosphites.

(Position of bands in cm.$^{-1}$; s = strong, m = medium, w = weak, b = broad.)

Dimethyl hydrogen phosphite.		Diethyl hydrogen phosphite.		Di*iso*propyl hydrogen phosphite.	
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
505 s		517 s		504	
554 s		555 s		538 m	
759	762 s		737 s	560 s	
777		760 ?			720 s
795 s		780 ?		760	765 w
825 m		795 s	802 ?	775	
985 s	990 m	822 ?		795 s	
1045 s		980 s		885	888 s
1080 m			1000 w	894	
1190 m	1199 w	1046 m		937	
1266 s	1258 m	1074		975 s	
1460	1458 s	1100	1100 m	1020	
2434 m.b.	2432 s.b.	1165		1053	
2856 m	2860 s	1261 s	1250 m	1110 m	1113 w
2922		1370		1146 m	1144
2962 s	2960 s	1392		1180 m	
2998	3010 m	1445	1445 s	1262 s	1258 m
		1480		1350 ?	1352 m
		2434 m.b.	2432 s.b.	1375	
		2851 ?		1390	
		2874		1458	1450 s
		2910 m		1468	
		2936 m	2940 s	2434 m.b.	2435 s.b.
		2981 s	2975 s	2852 ?	
				2880	2882 m
				2937 m	
				2981 s	2982 s

TABLE I (*continued*).

Trimethyl phosphite.				Triethyl phosphite.			
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
516 m	509 s	1462	1458 s	536 m		1265	1272 ?
552			2785	555		1275	
738	744 s.b.	2838 s	2840 s	737	740 s	1390	
775		2902 m		772		1445	1445 s
795 s		2946 s	2942 s	795 s		1478	
1014 s	1015 s	2990 m	2985 m	918 s		2764	
1060 m	1058 m			942 m		2821	
1088				1035 s	1030 m	2888 m	2874 s
1121				1061		2903 m	
1183 s				1097	1095 m	2933 s	2928 s
1265				1163		2981 s	2975 s

TABLE II.

Phosphonates.

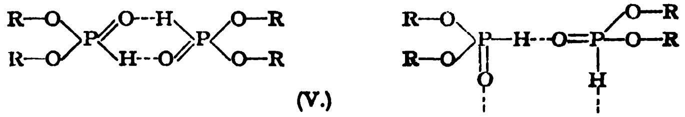
(Position of bands in cm.$^{-1}$; s = strong, m = medium, w = weak, b = broad.)

Dimethyl methylphosphonate.		Diethyl methylphosphonate.		Di*iso*propyl methylphosphonate.	
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
	300 ?	485	470 w	504 s	495 m
463		502 s			710 s
500 s	495 m		715 s	794 m	793
	706 s	771 m		898	880 m
789 s	788 m	806 s		918	915 w
822 s	816 m	898 s		983 s	
897 m		939		1008 s	
913 s		965 s		1034	
1032 s	1072 w	1023 s		1059	
1060 s	1057 w	1049 s		1112 m	1102 m
1185 m		1099 s	1100 m	1146 m	1140 w
1241 s	1240 m	1164 m		1180 m	
1256 ?		1250 s	1239 m	1248 s	1240 m
1315 m		1314 s		1315 m	
1419	1421 m	1365		1375	1350 m
1463	1465 m	1390		1390	
2864 s	2851 m	1420		1420	
2938 m	2929 s	1448	1445 m	1458	1445 s
2966 s	2961 w	1480		1468	
2989 s	2990 s	2863			2778 m
		2885	2880 w	2851	2835 w
		2923 m		2879	2870 m
		2943 m	2935 s	2934 m	2930 s
		2995 s	2990 s	2983 s	2985 s

Diethyl ethylphosphonate.				Di*iso*propyl ethylphosphonate.			
Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.	Infra-red.	Raman.
483 s	500 w	1254 s		485		1165	
522 s		1292	1288 m	504	502 w	1180	
	699 s	1367		545 s		1224 s	
742		1392			700 s	1251 m	
777 m		1420 ?		778		1286	
794 s		1448		796 s		1375	
815	811 w	1460	1460 s	887	890 m	1388	
938		1480		897		1418	
958 s		2853		959		1450	1450 s
1010	996 ?	2893	2895 w	986 s		1460	
1026 s		2914 m		1008		1469	
1042	1040 w	2945 m	2940 s	1023		2855	
1060		2985 s	2990 s	1042		2889	2890 w
1098	1100 m			1059		2942 m	2940 s
1165				1107	1100 m	2983 s	2985 s
1230 s	1230 w			1142			

The very broad nature of the infra-red band at 2435 cm.$^{-1}$ and the equally broad and diffuse nature of the corresponding Raman line suggest that in the liquid state this P—H bond may be associated in a bridge through oxygen atoms similar to the familar hydrogen bridge in

- -O—H- - - O or -N—H- - - O- systems, in this case leading to structures such as (V). Measurements with dilute solutions are now being planned to examine this further.



(V.)

We may now consider other correlations involving the P—O—C skeleton. A previous suggestion for phosphites and phosphonates based upon a few isolated measurements (Thompson, *J.*, 1948, 328) must now be regarded as invalid, since it is not borne out by the present results and can now be interpreted in another way. All the compounds except the trialkyl phosphites have an intense band at 1250—1260 cm.$^{-1}$, although in the more complex derivatives a doubling occurs here. It seems very probable that this band is associated with the stretchings of the P═O linkage. In the case of phosphorus oxychloride, $POCl_3$, the Raman frequency of 1295 cm.$^{-1}$ has been assigned to this vibration (Yost and Anderson, *J. Chem. Physics*, 1934, **2**, 624), and there is usually a corresponding Raman frequency with the phosphites and phosphonates, as was also pointed out by Arbusov, Batuev, and Vinogradova (*Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **54**, 599).

All the compounds now measured have a band near 795 cm.$^{-1}$, with the exception of diethyl methylphosphonate where a splitting seems to occur. This frequency also occurs in some of the Raman spectra. It may be attributed to a vibration which is largely controlled by the stretching of the P—O bond in the skeleton P—O—C, and having regard to the change in reduced mass would fall roughly into line with the corresponding frequencies for C—O and Si—O bands found previously (Thompson and Torkington, *J.*, 1945, 640; Richards and Thompson, *J.*, 1949, 124). Although this correlation is still uncertain, a further argument in support of it is found in the result that when a dialkyl hydrogen phosphite hydrolyses in damp air, the band at 795 cm.$^{-1}$ disappears, as the skeleton undergoes the important change -P—O—C to -P—O—H.

The absorption bands in the region 2800—3000 cm.$^{-1}$, which are connected with stretching vibrations of C—H bonds, reveal a close parallelism between the different compounds examined. It is clear that there are frequencies typical of CH_3 and CH_2 groups which may also differ slightly according to whether they are attached to carbon or to phosphorus. The spectra of all the compounds containing two or three methoxy-groups have an infra-red band at 2840—2860 cm.$^{-1}$ lying lower than the remainder, and the location and relative intensities of the other bands between 2900 and 3000 cm.$^{-1}$ are closely parallel with the alkyl radicals concerned. It may also be noted that examination of the region 1350—1500 cm.$^{-1}$, where the deformation vibrations of alkyl groups occur, reveals similar regularities. The differences are so well marked as to be a possible means for the identification and estimation of the alkyl groups concerned.

In the other parts of the spectrum there are some regularities which suggest possible correlation rules, but with less convincing precision. The dialkyl hydrogen phosphites have a strong band near 550 cm.$^{-1}$, and in addition all the compounds have a band near 500 cm.$^{-1}$. Between 900 and 1200 cm.$^{-1}$ there will be skeleton vibrations controlled by -C—O and possibly -P—C bonds. Here too, some regularities occur according to the alkoxy-radicals concerned, but the situation is complex. In some respects the position is similar to that found in esters and alkoxysilanes. The derivatives containing *iso*propyl radicals show very similar spectra between 850 and 1050 cm.$^{-1}$.

It is evident that interesting comparisons may be made if the extinction coefficients of some of the key bands are determined. It may then be possible to correlate the ionic character of bonds such as P═O, S═O, and N═O, or P—O and C—O. These measurements are now to be carried out with vapours and solutions.

We are indebted to Dr. A. Childs for the compounds examined, and we thank the Chief Scientific Officer, Ministry of Supply, for permission to publish the results.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 28th,* 1949.]

54. *Researches on Acetylenic Compounds. Part XXII. The Reaction Between Nickel Carbonyl and Monosubstituted Acetylenic Compounds.*

By E. R. H. JONES, T. Y. SHEN, and M. C. WHITING.

The reaction between monosubstituted acetylenes (RC≡CH), nickel carbonyl, and water in the presence of acids leads to the formation of α-substituted acrylic acids [$RC(CO_2H){=}CH_2$]. The application of this reaction to various types of acetylenic alcohol has been studied; the expected substituted acrylic acids are obtained, but with αβ-acetylenic carbinols [*e.g.* CHPr(OH)·C≡CH], it is preferable to employ the acetates rather than the free alcohols, and the products from βγ-acetylenic carbinols [*e.g.*, $CH_2(OH){\cdot}CH_2{\cdot}C{\equiv}CH$] cyclise spontaneously to lactones. In this way the synthesis of the naturally occurring antibiotic, α-methylenebutyrolactone, has been achieved. The behaviour of certain other monosubstituted acetylenes has been examined, and some conclusions relating to the part played by water in the reaction are drawn.

CERTAIN reports on wartime work by W. Reppe and his co-workers (B.I.O.S. Final Reports Nos. 266, 355, and 358; see also *Experientia*, 1949, **5**, 93) contain brief descriptions of a novel reaction in which acetylenic compounds are treated either with nickel carbonyl and an acid at about 40° ("stoicheiometric process") or with carbon monoxide under pressure at 100—180° in the presence of a nickel halide ("catalytic process"). In each case a compound possessing an active hydrogen atom, *e.g.*, water or an alcohol, is also present. The overall equations are given as:

Stoicheiometric

$$4RC{\equiv}CH + Ni(CO)_4 + 4EtOH + 2HCl = 4RC(CO_2Et){=}CH_2 + NiCl_2 + H_2$$

Catalytic

$$RC{\equiv}CH + CO + EtOH \underset{\text{halide}}{\overset{\text{Ni}}{=}} RC(CO_2Et){=}CH_2$$

It is implied that when carbon monoxide and a nickel halide are used nickel carbonyl is formed *in situ* and is the effective catalyst, and that the two methods are essentially similar. Acrylic acid or its derivatives are formed from acetylene itself, and it is stated that mono- and di-substituted acetylenes give, respectively, α-substituted and αβ-disubstituted acrylic acids, unsymmetrical disubstituted acetylenes giving a mixture of the two possible products. It is claimed that alcohols, water, amines, and thiols can be used as the active-hydrogen-containing component, and that a wide variety of acetylenes may be employed; however, except in the case of acetylene itself, no experimental details are given.

The reaction between some monosubstituted acetylenes (mostly alcohols of various types), nickel carbonyl, and water in the presence of acids ("stoicheiometric process") has been examined, partly in order to prepare some otherwise inaccessible αβ-unsaturated lactones and hydroxy-acids of possible biological interest (cf. Haynes, *Quarterly Reviews*, 1948, **2**, 46) and partly in an attempt to obtain information concerning the mechanism of this reaction. Work directed towards the second end is still in progress, and the present contribution is concerned only with the preparative aspect of the reaction and with the part played in it by water. Once a moderately satisfactory technique for effecting the reaction had been evolved it was applied to a variety of compounds with little variation; the conditions employed are therefore to some extent arbitrary.

Because of the lack of information on the German work, reactions with the hydrocarbons, hex-1-yne and phenylacetylene, were first carried out. When either of these was dissolved in a mixture of ethanol and concentrated hydrochloric acid and treated with an alcoholic solution of nickel carbonyl at about 55° an exothermic reaction took place after a short induction period. The proportions of the reactants were in accordance with the equation already given except that ethanol was used in large excess as the solvent and, because of the difficulty of weighing accurately small quantities of nickel carbonyl, a moderate (10—25%) excess was always employed. Isolation of the neutral fraction at the end of the reaction gave ethyl α-butylacrylate and ethyl atropate, each in about 50% yield; in the case of phenylacetylene it was also possible to isolate a small quantity (5% yield) of atropic acid, presumably in equilibrium with the ester. None of the starting material was recoverable in either case.

When this method was applied to representative αβ-acetylenic carbinols (propylethynylcarbinol and 1-ethynyl*cyclo*hexanol) however, no exothermic reactions were observed, no appreciable yields of the expected hydroxy-esters were obtained, and in both cases considerable amounts of the starting materials were recovered. In an endeavour to find satisfactory methods for these compounds numerous procedures were examined, including the addition of quinol or alternatively of benzoyl peroxide to the reaction mixture, and the use of the acetate in place of the carbinol itself, both under the normal conditions and (in the expectation of obtaining a mixed anhydride; cf. the German work) with the ethanol replaced by glacial acetic acid. In all these cases no exothermic reaction was observed; but when propylethynylcarbinol in *n*-propanol and acetic acid was treated with nickel carbonyl at 95° a violent reaction took place, and distillation of the neutral fraction gave some heterogeneous high-boiling material. Finally it was found that the acetate of propylethynylcarbinol (I) underwent a smooth exothermic reaction in ethanol containing acetic acid, although the induction period was rather lengthy unless a temperature of about 70° was used. Surprisingly, distillation of the neutral fraction of the reaction product gave very little volatile material, which moreover was heterogeneous. The acidic fraction on the other hand was appreciable in quantity and crystallised readily, giving the *acetoxy-acid* (II), m. p. 69°, in 40% yield.

$$\text{(I.)}\quad \mathrm{CHPr(OAc)\cdot C{\equiv}CH} \longrightarrow \mathrm{CHPr(OAc)\cdot C(CO_2H){=}CH_2}\quad \text{(II.)}$$

It was concluded that in this reaction, since the free acid and not the ester was formed, water must be involved. When the requisite amount of water was added to the alcohol used the yield was improved to 48%.

This technique, *i.e.*, the use of ethanol as solvent, glacial acetic acid in slight excess, and 0·5—2 molecular equivalents of water (within these limits the amount used appeared to be immaterial) with a reaction temperature of about 70°, was now applied to a number of acetylenes. It gave satisfactory yields of the free acids (35% and 48%) with the hydrocarbons, hex-1-yne and phenylacetylene, and also with the acetates of phenylethynylcarbinol (50%) and propargyl alcohol (40%). The tertiary carbinyl acetates derived from dimethylethynylcarbinol and 1-ethynyl*cyclo*hexanol, however, still failed to react exothermally, although in the latter case isolation of the acidic fraction of the reaction mixture gave a very small yield of the expected *acetoxy-acid* (III; $R_1R_2 = [CH_2]_5$, $R_3 = Ac$), m. p. 98·5°. Rather unexpectedly propargyl alcohol reacted exothermally under these conditions, but the isolation of the product, presumably

$$\mathrm{R_1R_2C(OR_3)\cdot C(CO_2H){=}CH_2}\quad \text{(III.)}$$

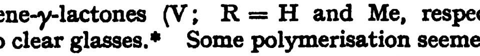
the somewhat unstable and very water-soluble hydroxy-acid (III; $R_1 = R_2 = R_3 = H$), was not possible. Phenylethynylcarbinol itself failed to react exothermally, but isolation of the acidic fraction of the reaction product gave a 10% yield of the expected *hydroxy-acid* (III; $R_1 = Ph$; $R_2 = R_3 = H$), accompanied by much syrupy, acidic material.

It therefore appears that with αβ-acetylenic carbinols and their acetates the reaction can proceed either exothermally and in good yield, or slowly without visible evolution of heat and in poor yield. The first type of reaction is observed with propargyl acetate and probably propargyl alcohol, and with secondary carbinyl acetates; the second with free secondary carbinols, tertiary carbinols, and tertiary carbinyl acetates.

The products thus obtained from the α-carbinols and their acetates showed the expected properties (hydrolysis and alcoholysis of the acetyl groups, esterification, etc.). Perhaps the most interesting was the compound (III; $R_1 = R_2 = H$; $R_3 = Ac$), m. p. 53°, prepared from propargyl acetate. This was hydrolysed with barium hydroxide solution to the corresponding *hydroxy-acid* which showed a strong tendency to polymerise, *e.g.*, during an attempted isolation by continuous extraction of an aqueous solution with ether. The polymer proved to be insoluble in methanol and acetone but readily soluble in water. Its *methyl* ester, prepared by treating the acetoxy-acid with methanolic sulphuric acid, is closely related to methyl methacrylate. Like the hydroxy- and acetoxy-acids it was found to be much less stable than analogues derived from secondary acetylenic carbinols.

When the method first used, *i.e.*, ethanol–hydrochloric acid at 55°, was applied to the βγ-acetylenic carbinols, but-3-yn-1-ol and pent-4-yn-2-ol (IV; R = H and Me), an exothermic reaction took place in both cases, and distillation of the neutral fractions of the reaction mixtures

(IV.)



$$\mathrm{RCH(OH)\cdot CH_2\cdot C{\equiv}CH} \longrightarrow \mathrm{R\underset{\displaystyle O\!-\!-\!-\!-\!-\!-}{CH}\cdot CH_2\cdot \underset{\displaystyle CO}{C}{=}CH_2}$$

(V.)

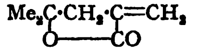
gave the two α-methylene-γ-lactones (V; R = H and Me, respectively) as liquids which polymerised on storage to clear glasses.* Some polymerisation seemed to take place during the reaction, and it was suspected that the products were somewhat impure. When the aqueous–ethanolic acetic acid technique was employed in these two cases no polymer was formed, and the two lactones obtained (yields 23% and 30%, respectively) proved to be homogeneous; the refractive indices differed slightly from those of specimens obtained by the hydrochloric acid method. They could be kept at room temperature for several weeks, or indefinitely when quinol was added. It is noteworthy that (V; R = H; " α-methylenebutyrolactone ") was obtained by Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1946, **68**, 2332) by the hydrolysis of a presumably glycosidic precursor occurring in *Erythronium americanum*, and was found by them to exhibit weak antibacterial properties. More complex substances containing the α-methylenebutyrolactone grouping have been isolated from natural sources [Asahina and Asano, *J. Pharm. Soc. Japan*, 1927, **539**, 1 (*Chem. Abstracts*, 1928, **22**, 4470); Asano and Kanematsu, *Ber.*, 1932, **65**, 1174; Cavallito and Kirchner, *J. Amer. Chem. Soc.*, 1947, **69**, 3030], but no previous synthesis of this type of compound has been reported. The physical properties of the synthetic material agreed well with those recorded by Cavallito and Haskell (*loc. cit.*), but the synthetic lactone did not show the skin-irritant properties of the natural product. It is possible that the latter contained a trace of some other substance which was responsible for these, or that individual susceptibility varies widely.

On being heated to 100° in the presence of a little benzoyl peroxide the two lactones polymerised to clear, hard resins, softening at 160—190°.*

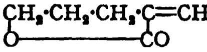
Attempts were made to improve the yield of α-methylenebutyrolactone by carrying out the nickel carbonyl reaction with the *acetate* of but-3-yn-1-ol, whereby the *acid* $AcO{\cdot}CH_2{\cdot}CH_2{\cdot}C(CO_2H){=}CH_2$ (p-*bromophenacyl* ester, m. p. 76°) was readily obtained in 47% yield. Attempts to hydrolyse this with alkali or to effect cyclisation to (V; R = H) by treatment with 1% methanolic sulphuric acid proved relatively unsuccessful since only moderate (30—60%) yields of rather impure lactone were obtained, apparently because of the instability of the latter towards mineral acids. This factor was probably responsible for the poor quality of the material obtained from but-3-yn-1-ol and nickel carbonyl when hydrochloric acid was used. As a further variant the hydroxyl group of but-3-yn-1-ol was protected by reaction with 2 : 3-dihydropyran (cf. Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246); the expected *ether* was readily obtained, but its reaction with nickel carbonyl gave only a 20% yield of the corresponding *acid*, the conversion of which into the methylenelactone (V) was therefore not studied.

In view of the differences between the primary, secondary, and tertiary types of αβ-acetylenic carbinols it was of interest to examine the behaviour of the tertiary βγ-acetylenic carbinol, 2-methylpent-4-yn-2-ol (Henbest, Jones, and Walls, *J.*, 1949, 2696). No exothermic reaction was observed, but after careful fractionation a 10% yield of the expected *lactone* (VI) was obtained. Its behaviour is thus similar to that of the secondary αβ-carbinol, phenylethynylcarbinol. The reaction with nickel carbonyl of the only γδ-acetylenic carbinol so far reported, pent-4-yn-1-ol (Lespieau, *Compt. rend.*, 1932, **194**, 287; Eglinton, Jones, and Whiting, forthcoming publication) was also examined. With this compound an exothermic reaction was observed, and the δ-lactone (VII) was obtained in 20% yield.

(VI.)



$$\begin{array}{l}Me_2C{\cdot}CH_2{\cdot}C{=}CH_2\\ \quad O\!\!-\!\!\!-\!\!\!-\!\!CO\end{array}$$



$$\begin{array}{l}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C{=}CH_2\\ O\!\!-\!\!\!-\!\!\!-\!\!\!-\!\!\!-\!\!\!-\!\!CO\end{array}$$

(VII.)

Concurrently with the work on acetylenic carbinols the application of the nickel carbonyl reaction to monosubstituted acetylenes of some other types was attempted. With the vinylacetylenic compounds, 2-methylpent-1-en-3-yne, 1-ethynyl*cyclo*hexene, pent-2-en-4-yn-1-ol, and pent-2-en-4-yn-1-yl acetate no exothermic reactions were observed either in ethanolic hydrochloric acid or in aqueous–ethanolic acetic acid. In the case of 1-ethynyl*cyclo*hexene under the latter conditions, isolation of the acidic fraction gave only a 1·5% yield of a high-melting solid clearly not the expected acid. No exothermic reaction was observed with phenyl ethynyl ketone (acetic acid technique); as was the case with the reactions involving vinylacetylenes, much dark polymeric material was formed.

In this communication the results of investigations, as yet incomplete, with various disubstituted acetylenes, and on the mechanism of the reaction, will not be discussed. However, even at this stage it can be pointed out that it is almost certainly the free acids, and not the esters, which are formed initially in this reaction, and the presence of water (either added to the reaction mixture or formed *in situ* in side reactions) is necessary. This is convincingly demonstrated by the fact that even when carefully dried ethanol is employed as solvent in experiments employing acetic acid, the free acid and not the ester is the principal product. In most reactions a little ester is also formed (its isolation is usually difficult and was not generally attempted) but this is in all probability the result of subsequent esterification, which of course takes place to equilibrium when a mineral-acid catalyst is present. When dried alcohol was used as solvent the yields of crystalline acids in the cases of phenylacetylene and phenylethynylcarbinyl acetate were reduced to 30% and 24%, respectively (normally 48% and 50%). If it is assumed that the hydrogen formed in the reaction according to the equation given by Reppe is converted into water a 25% yield of the acid would be possible.*

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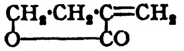
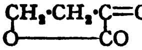
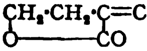
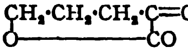
* Patents applied for (B.P. Applications, 7091 and 7092/48).

The light-absorption properties of the acids and lactones obtained are shown below.

Compound.	λ, A.	ε.
$CH_2(OH)\cdot C(CO_2H){=}CH_2$	2140 2300	3000 300
$CHPr(OH)\cdot C(CO_2H){=}CH_2$	2150 2450	6500 1300
$CHPh(OH)\cdot C(CO_2H){=}CH_2$	2170 2380	7000 1800
$[CH_2]_5{>}C(OH)\cdot C(CO_2H){=}CH_2$	2190 2250	4000 1200
$[CH_2]_5{>}C(OAc)\cdot C(CO_2H){=}CH_2$	2170 2320	4000 900
 $\begin{array}{l}CH_2\cdot CH_2\cdot C{=}CH_2\\ O\text{———}CO\end{array}$	2200 2250	5000 500
 $\begin{array}{l}CH_2\cdot CH_2\cdot C{=}CH_2\\ O\text{———}CO\end{array}$ (in water)	2200 [1] 2250 2350 2400 2450	7500 5000 900 400 250
 $\begin{array}{l}CH_2\cdot CH_2\cdot C{=}CH_2\\ O\text{———}CO\end{array}$ (in water) [2]	2300 2350 2400	2400 900 500
 $\begin{array}{l}CH_2\cdot CH_2\cdot CH_2\cdot C{=}CH_2\\ O\text{————}CO\end{array}$ (in water)	2200 [1] 2250 2300 2350 2400 2450	5700 4450 3100 1750 1000 470

None of the above compounds exhibited any maximal absorption in the range examined.

Except where otherwise stated alcoholic solutions were employed and a Hilger Medium Spectrograph was used.

[1] Beckman spectrograph used. [2] Cavallito and Haskell, *loc. cit.*

EXPERIMENTAL.

General Method.—The apparatus consisted of a flask of 250 c.c. capacity equipped with a thermometer whose bulb dipped into the liquid in the flask, a mercury-seal stirrer, a reflux condenser, a gas inlet, and a dropping funnel. The acetylenic compound, the solvent, the acid used, and in some cases water were stirred under nitrogen while the flask was heated with a free flame until the liquid reached the desired temperature (55—80°). About 2 c.c. of the solution of nickel carbonyl were added and, after an induction period of variable length, the reaction began, as shown by a marked rise in temperature and in some cases a transient deep-brown coloration. The remainder of the carbonyl solution was then added dropwise at such a rate that the temperature remained constant until the reaction was complete, when the temperature began to fall. As soon as the reaction mixture was sufficiently cool, ether (5—10 times the volume of nickel carbonyl used) was added, the apparatus was adapted for distillation, and the flask was warmed on the steam-bath until everything volatile under these conditions had distilled. The distillate was poured away carefully.

Up to this stage all operations were carried out in a well-ventilated fume-cupboard, but when the excess of nickel carbonyl had been removed the reaction mixture could be handled in the open laboratory. The solution was poured into dilute sulphuric acid and extracted with ether or chloroform; the extract was washed thoroughly with sodium hydrogen carbonate solution, and the neutral and acidic fractions were isolated, the procedure varying from case to case.

Ethyl Atropate.—The reaction was carried out by the general method, using phenylacetylene (20·6 g.), ethanol (60 c.c.), and concentrated hydrochloric acid (8 c.c.), to which a solution of nickel carbonyl (6·6 c.c.) in ethanol (20 c.c.) was added. The temperature was kept at 55° by occasional external cooling. The acid fraction gave, after crystallisation from water, atropic acid (1·5 g.), m. p. 105—106°; the neutral portion was distilled giving the ester (16·7 g.), b. p. 57—63°/10^{-3} mm., n_D^{23} 1·5229 (Auwers and Eisenlohr, *J. pr. Chem.*, 1911, **84**, 89, give b. p. 120·2—120·4°/14 mm., n_D^{16} 1·5260).

Ethyl α-Butylacrylate.—Hex-1-yne (16·4 g.), ethanol (60 c.c.), and concentrated hydrochloric acid (9 c.c.) reacted at 50—70° with a solution of nickel carbonyl (8 c.c.) in ethanol (20 c.c.). Isolation with pentane gave ethyl α-butylacrylate (16·0 g.), b. p. 66°/10 mm., n_D^{20} 1·4290 (Blaise and Luttringer, *Bull. Soc. chim.*, 1905, **33**, 778, give b. p. 177°).

Atropic Acid.—(*a*) The reaction was carried out by the general method at 70° using phenylacetylene (15·3 g.), acetic acid (6 c.c.), ethanol (30 c.c.), water (2 c.c.), and a solution of nickel carbonyl (6 c.c.) in ethanol (15 c.c.). Isolation of the acidic fraction followed by crystallisation from light petroleum (b. p. 60—80°) gave atropic acid (10·65 g., 48%) as prismatic needles, m. p. 106—107° (Fittig and Wurster, *Annalen*, 1879, **195**, 147, give m. p. 106—107°). From the mother-liquors a solid (380 mg.), m. p. 89—90°, was obtained by crystallisation. Recrystallisation of this from light petroleum (b. p. 60—80°) gave irregular rhombic plates, m. p. 86—87° undepressed on admixture with atropic acid (mixed m. p. 90—94°) (Found: C, 73·65, 71·75; H, 5·45, 5·4%). Light absorption: Maxima at 2600 and 2800 A., $E^{1\%}_{1\,\text{cm.}}$ = 430 and 330, respectively (cf. atropic acid, which has a maximum at 2500 A., $E^{1\%}_{1\,\text{cm.}}$ = 350, and end absorption). The constitution of this solid was not investigated further.

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* Since writing the above account it has been found that an exothermic reaction takes place on adding nickel carbonyl to a solution of phenylacetylene and glacial acetic acid in dry anisole at 60°, atropic acid being obtained in 20% yield. In this case the water required must clearly be formed in side-reactions involving nickel carbonyl and the acetylene, since none could be formed from the solvent mixture alone.

(*b*) Repetition of this experiment using ethanol dried over magnesium ethoxide, and omitting the water gave crude atropic acid, m. p. 101—103° (6·65 g.). Crystallisation of this material gave the pure acid, m. p. 106—107° (5·6 g., 30%).

a-Butylacrylic Acid.—Hex-1-yne (41 g.), ethanol (100 c.c.), glacial acetic acid (15 c.c.), and water (7 c.c.), reacted with a solution of nickel carbonyl (17 c.c.) in ethanol (50 c.c.) at *ca.* 67° by the general method in a 1-l. flask. Isolation of the acidic fraction followed by distillation gave *a*-butylacrylic acid (21·75 g.), b. p. 69—70°/0·2 mm., $n_D^{19.5}$ 1·4453 (Blaise and Luttringer, *loc. cit.*, give b. p. 109—110°/10 mm.).

3-*Acetoxyhex*-1-*ene*-2-*carboxylic Acid* (II).—Propylethynylcarbinyl acetate (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 45) (9·3 g.), ethanol (20 c.c.), glacial acetic acid (5 c.c.), and water (1 c.c.) reacted at 74—78° by the general method with nickel carbonyl (3 c.c.) in ethanol (10 c.c.). Isolation of the acidic fraction with chloroform, followed by evaporation of the solvent, gave a residue which solidified when scratched and, on crystallisation from light petroleum (b. p. 40—60°), gave a product (5·9 g., 48%), m. p. 67°. Recrystallisation from the same solvent gave the *acetoxy-acid* as long needles, m. p. 68·5° (Found: C, 58·2; H, 7·6. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%).

3-*Hydroxyhex*-1-*ene*-2-*carboxylic Acid* (III; $R_1 = R_3 = H$, $R_2 = Pr$).—The acetoxy-acid (3 g.) was dissolved in a solution of potassium hydroxide (3 g.) in water (6 c.c.) with cooling. After 18 hours at 20° the solution was acidified; isolation with ether followed by distillation at 80° (bath temp.)/10^{-4} mm. gave the *hydroxy-acid* (1·65 g.) as a syrup, n_D^{22} 1·4685 (Found: C, 58·35; H, 8·75. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%). The *ethyl* ester was prepared by heating the hydroxy-acid (2·5 g.), ethanol (12 c.c.), and concentrated sulphuric acid (0·6 c.c.) under reflux for three hours. Isolation of the product with ether and distillation gave the ester (2·3 g.), b. p. 95°/5·5 mm., n_D^{18} 1·4521 (Found: C, 62·75; H, 9·6. $C_9H_{16}O_3$ requires C, 62·75; H, 9·35%). The ethyl ester *a-naphthylurethane*, prepared at room temperature, formed felted needles, m. p. 88°, from light petroleum (b. p. 60—80°) (Found: N, 4·1. $C_{20}H_{23}O_4N$ requires N, 3·95%).

3-*Acetoxy*-3-*phenylprop*-1-*ene*-2-*carboxylic Acid* (III; $R_1 = H$, $R_2 = Ph$, $R_3 = Ac$).—Phenylethynylcarbinyl acetate (Jones and McCombie, *J.*, 1942, 733) (11·6 g.), ethanol (20 c.c.), glacial acetic acid (3 c.c.), and water (2 c.c.) reacted at 70° by the general method with nickel carbonyl (3 c.c.) in ethanol (10 c.c.). Isolation of the acidic fraction with ether gave an oil which soon solidified; crystallisation from light petroleum (b. p. 60—80°) gave the *acetoxy-acid* (7·4 g., 50%) as stout needles, m. p. 110·5° unchanged on recrystallisation from the same solvent (Found: C, 65·45; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·25; H, 5·55%).

3-*Hydroxy*-3-*phenylprop*-1-*ene*-2-*carboxylic Acid* (III; $R_1 = R_3 = H$, $R_2 = Ph$).—(*a*) The acetoxy-acid (3 g.) was dissolved in a solution of sodium hydroxide (2 g.) in water (20 c.c.). After storage at 20° for 48 hours, acidification and isolation with ether gave a syrup which was induced to crystallise by keeping it for several hours at 35°. Recrystallisation from benzene gave a product (2·0 g.), m. p. 79—80°; after further recrystallisation from the same solvent the *hydroxy-acid* formed fine needles, m. p. 81° (Found: C, 67·15; H, 5·55. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·65%).

(*b*) Phenylethynylcarbinol (18·3 g.), ethanol (30 c.c.), glacial acetic acid (6 c.c.), and water (2 c.c.) were heated to 80° and maintained at about this temperature while a solution of nickel carbonyl (6 c.c.) in ethanol (15 c.c.) was added in small portions during 20 minutes. No exothermic reaction took place; isolation of the acidic fraction with ether gave a syrup (7·0 g.) whose benzene solution, on addition of light petroleum (b. p. 60—80°) and seeding with material obtained by method (*a*), gave the crude hydroxy-acid (3·1 g.), m. p. 72—75°. After recrystallisation from benzene this had m. p. 81°, undepressed on admixture with a specimen prepared by method (*a*).

3-*Acetoxyprop*-1-*ene*-2-*carboxylic Acid* (III; $R_1 = R_2 = H$, $R_3 = Ac$).—Propargyl acetate (6·5 g.), ethanol (20 c.c.), glacial acetic acid (3 c.c.), and water (1 c.c.) were heated to 70°, and a solution of nickel carbonyl (3 c.c.) in ethanol (10 c.c.) was added, the temperature being maintained at about 75°. After removal of the excess of nickel carbonyl, ether (100 c.c.) was added, and the solution was shaken with a solution of concentrated sulphuric acid (1 c.c.) in water (10 c.c.), which was then extracted with ether (2 × 20 c.c.). The combined ethereal extracts were shaken with a slight excess of a saturated solution of potassium hydrogen carbonate, which was acidified with concentrated hydrochloric acid. After being decanted from the precipitate of potassium chloride, which was washed well with ether, the aqueous solution was extracted with ether (5 × 150 c.c.). Evaporation of most of the solvent from the dried extract through an 8-inch Lapworth column and the removal of the remainder under reduced pressure below 20° gave an oil which readily solidified; crystallisation from light petroleum (b. p. 40—60°) containing a little benzene gave a product (3·1 g.), m. p. 49—50°; a further 0·6 g. of less pure material, m. p. 44°, was obtained from the filtrate. After recrystallisation from light petroleum (b. p. 40—60°) the *acetoxy-acid* formed nacreous leaflets, m. p. 53° (Found: C, 50·2; H, 5·8. $C_6H_8O_4$ requires C, 50·0; H, 5·6%).

3-*Hydroxyprop*-1-*ene*-2-*carboxylic Acid* (III; $R_1 = R_2 = R_3 = H$).—The acetoxy-acid (2·05 g.) was dissolved in a solution of barium hydroxide (4 g.) in water (40 c.c.). After 24 hours the solution was brought to pH *ca.* 2·5 by adding sulphuric acid; after filtration it was found to give no precipitate with barium chloride solution and only a very faint turbidity with sulphuric acid. Evaporation under reduced pressure and distillation at 60—75° (bath temp.)/10^{-4} mm. gave the *hydroxy-acid* (530 mg.), n_D^{19} 1·4760 (Found: C, 46·4; H, 6·4. $C_4H_6O_3$ requires C, 47·05; H, 5·95%).

Methyl 3-*Hydroxyprop*-1-*ene*-2-*carboxylate.*—The acetoxy-acid (2·5 g.), methanol (15 c.c.), and concentrated sulphuric acid (0·5 c.c.) were heated under reflux for five hours. Ether (25 c.c.) was added and the solution was washed with a solution of potassium carbonate (1·5 g.) in water (2 c.c.), the aqueous layer being extracted with ether (2 × 5 c.c.). The combined extracts were partly dried (Na_2SO_4), and the ether and methanol were evaporated off through an 8-inch Lapworth column. The residue contained a large quantity of water; chloroform and sodium sulphate were added, and, after some time, the latter was separated and the chloroform was distilled off through a column. Distillation of the residue gave the *methyl* ester, b. p. 81°/9 mm., n_D^{16} 1·4548 (Found: C, 51·6; H, 6·85. $C_5H_8O_3$ requires C, 52·2; H, 6·8%).

α-1-*Acetoxy*cyclo*hexylacrylic Acid* [III; $R_1R_2 = (CH_2)_5$, R_3 = Ac].—1-Ethynyl*cyclo*hexyl acetate (Rupe, Messner, and Kambli, *Helv. Chim. Acta*, 1928, **11**, 453) (11·1 g.), dry ethanol (20 c.c.), and glacial acetic acid (3 c.c.) were heated to 75° and maintained at about that temperature for 15 minutes while a solution of nickel carbonyl (3 c.c.) in ethanol (10 c.c.) was added in small portions Isolation of the acidic portion of the resulting mixture with ether gave a syrup which was dissolved in light petroleum and cooled to 0°. On storage, a rather gummy solid (700 mg.) was obtained, which by crystallisation from light petroleum (b. p. 60—80°) gave the *acetoxy-acid* as stout prismatic needles (500 mg.), m. p. 98·5° unchanged on recrystallisation from the same solvent (Found: C, 62·3; H, 7·6. $C_{11}H_{16}O_4$ requires C, 62·25; H, 7·6%).

α-1-*Hydroxy*cyclo*hexylacrylic Acid* [III; $R_1R_2 = (CH_2)_5$, R_3 = H].—α-1-Acetoxy*cyclo*hexylacrylic acid (200 mg.) was dissolved in a solution of potassium hydroxide (300 mg.) in water (1 c.c.). After 18 hours, isolation of the acidic fraction with ether gave an oil which crystallised after about two weeks at 20°. Recrystallisation from light petroleum (b. p. 60—80°), in which it was rather soluble, gave the *hydroxy-acid* (85 mg.) as acicular prisms, m. p. 78—81°. Further recrystallisation from the same solvent or from aqueous methanol did not alter the melting point; and more drastic conditions of hydrolysis did not improve the yield (Found: C, 63·85; H, 8·05. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%).

But-3-yn-1-yl Acetate.—Acetylation of but-3-yn-1-ol (IV; R = H) (46 g.) with acetic anhydride (69 c.c.) and pyridine (55 c.c.) with cooling, then for 20 hours at room temperature, gave the *acetate* (54·5 g., 75%), b. p. 65°/40 mm., n_D^{25} 1·4230 (Found: C, 64·0; H, 7·2. $C_6H_8O_2$ requires C, 64·25; H, 7·2%).

4-*Acetoxybut*-1-*ene*-2-*carboxylic Acid.*—But-3-yn-1-yl acetate (7·5 g.), ethanol (20 c.c.), water (0·6 c.c.), and glacial acetic acid (3 c.c.) reacted by the general method with a solution of nickel carbonyl (3 c.c.) in ethanol (20 c.c.). Isolation of the acidic fraction with ether gave a pale yellow oil (4·1 g.), n_D^{22} 1·4520, which was distilled to give the *acid acetate* (3·4 g.), b. p. 100°/0·05 mm., n_D^{24} 1·4515 (Found: C, 53·1; H, 6·65. $C_7H_{10}O_4$ requires C, 53·1; H, 6·35%). The p-*bromophenacyl* ester separated from aqueous methanol in flat needles, m. p. 76° (Found: C, 50·75; H, 4·4. $C_{15}H_{15}O_5Br$ requires C, 50·7; H, 4·25%).

4-(2-*Tetrahydropyranyloxy*)*but*-1-*yne.*—To a mixture of but-3-yn-1-ol (IV; R = H) (15·0 g.) and 2 : 3-dihydropyran (18·5 g.), concentrated hydrochloric acid (0·2 g.) was added. An exothermic reaction took place which was moderated by ice-cooling. After the solution had been kept for 18 hours at 20° potassium hydroxide (0·3 g.) was added, and the precipitated potassium chloride was filtered off; distillation then gave the *ether* (26 g.), b. p. 92—95°/18 mm., n_D^{18} 1·4589 (Found: C, 70·3; H, 9·65. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%).

4-(2-*Tetrahydropyranyloxy*)*but*-1-*ene*-2-*carboxylic Acid and its Ethyl Ester.*—The above ether (11·4 g.) in ethanol (25 c.c.), glacial acetic acid (4 c.c.), and water (1·5 c.c.) reacted with a solution of nickel carbonyl (4 c.c.) in ethanol (10 c.c.) at 75°. The standard procedure was employed, an exothermic reaction taking place. Isolation of the acidic fraction then gave an oil (3·5 g.) of which a portion (2·2 g.) was distilled at 75° (bath temp.)/10^{-4} mm. to give the *acid* (1·8 g.), n_D^{15} 1·4773 (Found: C, 60·1; H, 8·05. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%). The neutral fraction was distilled to give the corresponding *ethyl* ester (1·5 g.), b. p. 82·5°/0·2 mm., n_D^{18} 1·4612 (Found: C, 63·2; H, 8·85. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·85%). Attempts to characterise the acid by preparation of crystalline *p*-nitrobenzyl and *p*-bromophenacyl esters proved unsuccessful.

4-*Hydroxybut*-1-*ene*-2-*carboxylic Acid Lactone* ("α-*Methylenebutyrolactone*") (V; R = H).—(*a*) But-3-yn-1-ol (IV; R = H) (10·5 g.), ethanol (30 c.c.), glacial acetic acid (6 c.c.), and water (2 c.c.) reacted at 80° with a solution of nickel carbonyl (6 c.c.) in ethanol (10 c.c.). The reaction began only after a lengthy induction period. After the excess of nickel carbonyl had been removed water was added, the solution was thoroughly extracted with ether, and the extract was washed with the minimum quantities of dilute sulphuric acid and sodium hydrogen carbonate solution. A little quinol was added at this stage. Evaporation of the solvent through an 8-inch Dufton column and distillation gave the lactone (3·4 g., 23%), b. p. 38°/0·2 mm., n_D^{22} 1·4707. Careful re-fractionation gave five fractions whose refractive indices were constant to within 0·0004 (Found: C, 60·9; H, 6·55. Calc. for $C_5H_6O_2$: C, 61·2; H, 6·15%) (Cavallito and Haskell, *loc. cit.*, give b. p. 57—60°/2 mm., n_D^{20} 1·470).

(*b*) A solution of nickel carbonyl (7 c.c.) in methanol (15 c.c.) was added to but-3-yn-1-ol (10·5 g.) in methanol (40 c.c.) and concentrated hydrochloric acid (6 c.c.) at 60°. An exothermic reaction took place; isolation of the neutral fraction (care being taken to remove powdery polymer by decantation) followed by distillation gave the lactone (3 g.), b. p. 92—95°/13 mm., n_D^{21} 1·4662. After a few days an elastic polymer was formed.

4-*Hydroxypent*-1-*ene*-2-*carboxylic Acid Lactone* (V; R = Me).—(*a*) Pent-4-yn-2-ol (IV; R = Me) (12·6 g.) reacted at 80° exactly as in the previous preparation [method (*a*)]. Distillation of the crude product gave the *lactone* (5·05 g.), b. p. 33°/0·02 mm., n_D^{18} 1·4596. Careful re-fractionation gave five fractions whose refractive indices were constant to within 0·0010 (Found: C, 64·5; H, 7·5. $C_6H_8O_2$ requires C, 64·25; H, 7·2%).

(*b*) The reaction was carried out by the general method at 50—55° using pent-4-yn-2-ol (12·6 g.) in methanol (45 c.c.) and concentrated hydrochloric acid (6 c.c.) and adding a solution of nickel carbonyl (5 c.c.) in methanol (15 c.c.). The reaction was strongly exothermic; isolation of the neutral fraction followed by distillation gave the lactone (7·1 g.), b. p. 87—90°/9 mm., which polymerised on storage.

4-*Hydroxy*-4-*methylpent*-1-*ene*-2-*carboxylic Acid Lactone* (VI).—2-Methylpent-4-yn-2-ol (Henbest, Jones, and Walls, *J.*, 1949, 2696) (15·8 g.) was dissolved in ethanol (30 c.c.), glacial acetic acid (7 c.c.), and water (3 c.c.), and the mixture was heated to 75—80° for 20 minutes during the addition of a solution of nickel carbonyl (8 c.c.) in ethanol (10 c.c.). No exothermic reaction was observed; isolation of the neutral fraction and distillation gave a product (3 g.), b. p. 40—64°/1·0 mm., n_D^{19} 1·4375—1·4541, which after careful refractionation gave the *lactone* (1·5 g.), b. p. 45°/1 mm., n_D^{17} 1·4561 (Found: C, 66·5; H, 8·0. $C_7H_{10}O_2$ requires C, 66·6; H, 8·0%).

5-Hydroxypent-1-ene-2-carboxylic Acid Lactone (VII). Pent-4-yn-1-ol (Eglinton, Jones, and Whiting, forthcoming publication) (12·6 g.) was dissolved in ethanol (20 c.c.), glacial acetic acid (6 c.c.), and water (2 c.c.), and the mixture was heated to 80°. A solution of nickel carbonyl (6 c.c.) in ethanol (10 c.c.) was added; an exothermic reaction began only after a long induction period. Isolation of the neutral fraction and careful fractional distillation gave the *lactone* (3·5 g.), b. p. 56·5°/0·07 mm., n_D^{18} 1·4810. This appeared to be homogeneous, but despite purification by repeated fractional distillation analytical results were inaccurate (Found: C, 63·25, 63·2; H, 7·55, 7·5. $C_6H_8O_2$ requires C, 64·25; H, 7·2%). Its light-absorption properties (see table) were normal.

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Imperial College of Science and Technology, London, S.W.7.
The University, Manchester, 13.
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55. *Researches on Acetylenic Compounds. Part XXIII. The Preparation and Properties of αβ-Acetylenic γ-Keto-esters.*

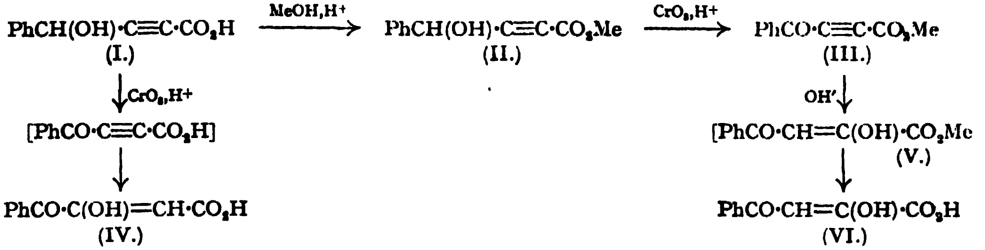
By E. R. H. Jones, T. Y. Shen, and M. C. Whiting.

Oxidation of the esters of αβ-acetylenic γ-hydroxy-acids with chromic acid in acetone gives the γ-keto-esters. On the other hand, oxidation of the free acids is accompanied by hydration of the triple bond resulting in the formation of βγ-diketo-acids; alkaline hydrolysis of a typical γ-keto-ester leads to hydration in the opposite direction, an αγ-diketo-acid being formed. With various types of amines, the keto-esters give adducts, convertible by mild acid hydrolysis into αγ-diketo-acid derivatives, and with hydrazine, hydroxylamine, and diazomethane the keto-esters yield the expected heterocyclic compounds.

As an extension of recent work on the synthesis of acetylenic hydroxy-acids (Haynes and Jones, *J.*, 1946, 503) and on the conversion of ethynylcarbinols into the corresponding ketones (Bowden, Heilbron, Jones, and Weedon, *J.*, 1945, 39), the application of the chromic acid–acetone-oxidation procedure to the hydroxy-acids and their esters has been investigated. No general synthesis of the expected acetylenic keto-esters has been described, although Nineham and Raphael (*J.*, 1949, 118) have prepared methyl β-benzoylpropiolate (see also Ingold, *J.*, 1925, 1199) and a vinylacetylenic keto-acid has been obtained by Heilbron, Jones, and Sondheimer (*J.*, 1949, 604) by oxidation of the corresponding primary-secondary glycol.

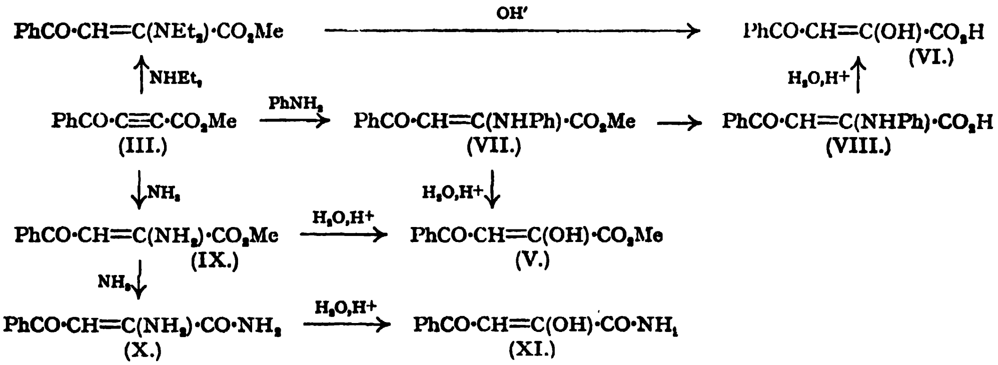
It was found that the method of Bowden, Heilbron, Jones, and Weedon (*loc. cit.*) was applicable generally to αβ-acetylenic hydroxy-esters, and *acylpropiolic esters*, $RCO{\cdot}C{\equiv}C{\cdot}CO_2Me$, have been prepared in the cases where R = Ph, Me, and Pr. They are pungent, somewhat lachrymatory, compounds which decompose readily on heating to 70—120°, and they resinify on treatment with pyridine. Their structures were confirmed by hydrogenation to known β-acylpropionic esters. Similarly, oxidation of the methyl ester of 5-hydroxyhex-3-en-1-yne-1-carboxylic acid gave the corresponding *keto*-ester ($MeCO{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CO_2Me$) as a very unstable liquid. When the same method was applied to the acetylenic hydroxy-acids themselves, however, oxidation was accompanied by hydration of the triple bond. Thus the hydroxy-acid (I) derived from phenylethynylcarbinol gave, in 40% yield, a crystalline acid which, in view of its analysis, light-absorption properties, ferric chloride coloration, and reaction with *o*-phenylenediamine to give a *quinoxaline* derivative, must be formulated as β-*hydroxy*-β-*benzoylacrylic acid* (IV) [cf. the hydration of phenyl ethynyl ketone to 1-phenylbutane-2 : 3-dione (Bowden, Braude, and Jones, *J.*, 1946, 945), which, however, requires mercuric sulphate catalysis]. The oxidation of 3-hydroxybut-1-yne-1-carboxylic acid also apparently proceeds with concomitant hydration since the unstable acidic product gave a strong ferric chloride coloration and yielded a *quinoxaline* derivative with *o*-phenylenediamine.

An obvious alternative route to the free αβ-acetylenic γ-keto-acids was by the hydrolysis of the corresponding esters. An exothermic reaction occurred on treatment of the ester (III) with aqueous methanolic potassium hydroxide and, after 24 hours α-hydroxy-β-benzoylacrylic acid (VI) (benzoylpyruvic acid) was isolated on acidification. Variable results were obtained on repetition of this alkaline hydrolysis, probably owing to the instability of the acid (VI). The ester (V) was presumed to be an intermediate in this reaction but attempts to isolate it were unsuccessful.



$$\begin{tikzcd}
\underset{\text{(I.)}}{\text{PhCH(OH)·C}\equiv\text{C·CO}_2\text{H}} \arrow[r, "\text{MeOH,H}^+"] \arrow[d, "\text{CrO}_3\text{,H}^+"] & \underset{\text{(II.)}}{\text{PhCH(OH)·C}\equiv\text{C·CO}_2\text{Me}} \arrow[r, "\text{CrO}_3\text{,H}^+"] & \underset{\text{(III.)}}{\text{PhCO·C}\equiv\text{C·CO}_2\text{Me}} \arrow[d, "\text{OH}'"'] \\
{[\text{PhCO·C}\equiv\text{C·CO}_2\text{H}]} \arrow[d] & & {[\text{PhCO·CH=C(OH)·CO}_2\text{Me}} \arrow[d, "\text{(V.)}"] \\
\underset{\text{(IV.)}}{\text{PhCO·C(OH)=CH·CO}_2\text{H}} & & \underset{\text{(VI.)}}{\text{PhCO·CH=C(OH)·CO}_2\text{H}}
\end{tikzcd}$$

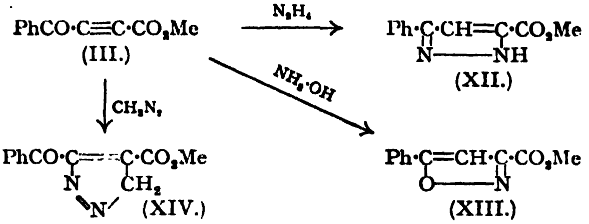
The keto-esters studied were found to react readily with amines (cf. Bowden, Braude, Jones, and Weedon, *J.*, 1945, 45). Thus methyl β-benzoylpropiolate (III), when treated with aniline, gave the crystalline *adduct* (VII) in 85% yield; the latter was hydrolysed to (V) with dilute mineral acids at room temperature, and hence has the structure shown, rather than that in which the anilino-group is in the β-position to the carbomethoxyl group. Alkaline hydrolysis gave the known acid (VIII), convertible into (VI). Treatment of methyl β-benzoylpropiolate with diethylamine gave an analogous liquid *adduct*. The reaction with ammonia was more complex; liquid ammonia caused resinification, but treatment of (III) in methanolic solution with aqueous ammonia resulted in an immediate exothermic reaction. Isolation of the product after some time gave the crystalline *amino-amide* (X) in 50% yield. When, however, the product was isolated by rapid removal of the ammonia and solvent immediately after the exothermic reaction had ceased, the *amino*-ester (IX), was obtained as a yellow oil which, after distillation at 70° (bath temp.)/10^{-4} mm., crystallised and then melted at 40°. Mild acid hydrolysis of (IX) and (X) proceeded as expected, the known enols (V) and (XI) being formed; the position of the amino-group was thus established.



$$\begin{tikzcd}
\text{PhCO·CH=C(NEt}_2\text{)·CO}_2\text{Me} \arrow[rr, "\text{OH}'"] & & \underset{\text{(VI.)}}{\text{PhCO·CH=C(OH)·CO}_2\text{H}} \\
\underset{\text{(III.)}}{\text{PhCO·C}\equiv\text{C·CO}_2\text{Me}} \arrow[u, "\text{NHEt}_2"'] \arrow[r, "\text{PhNH}_2"] \arrow[d, "\text{NH}_3"'] & \underset{\text{(VII.)}}{\text{PhCO·CH=C(NHPh)·CO}_2\text{Me}} \arrow[r] \arrow[d, "\text{H}_2\text{O,H}^+"] & \underset{\text{(VIII.)}}{\text{PhCO·CH=C(NHPh)·CO}_2\text{H}} \arrow[u, "\text{H}_2\text{O,H}^+"] \\
\underset{\text{(IX.)}}{\text{PhCO·CH=C(NH}_2\text{)·CO}_2\text{Me}} \arrow[r, "\text{H}_2\text{O,H}^+"] \arrow[d, "\text{NH}_3"'] & \underset{\text{(V.)}}{\text{PhCO·CH=C(OH)·CO}_2\text{Me}} & \\
\underset{\text{(X.)}}{\text{PhCO·CH=C(NH}_2\text{)·CO·NH}_2} \arrow[r, "\text{H}_2\text{O,H}^+"] & \underset{\text{(XI.)}}{\text{PhCO·CH=C(OH)·CO·NH}_2} &
\end{tikzcd}$$

The addition of ammonia to β-benzoylacrylic acid has recently been stated (Bougault and Chabrier, *Compt. rend.*, 1948, **226**, 1378), to give β-amino-β-benzoylpropionic acid, although no evidence was quoted in support of the structure assigned to the adduct. Such a result is surprising in view of an earlier discussion (Bougault, *Ann. Chim.*, 1908, **15**, 491) of the addition of nucleophilic reagents to this acid in which, by analogy with other reactions giving known α-substituted β-benzoylpropionic acids, it was considered probable that the adduct obtained from ammonia was α-amino-β-benzoylpropionic acid. Since it seems unlikely that addition of ammonia to corresponding ethylenic and acetylenic substances takes place in opposite directions, and the structure of the adduct from the latter has been unambiguously proved, the earlier interpretation of this reaction is perhaps to be preferred.

The formation of heterocyclic compounds by the reaction of ethynyl ketones with hydrazine, hydroxylamine, etc., has already been described (Bowden and Jones, *J.*, 1944, 953). The ester (III) gave with hydrazine and hydroxylamine the crystalline esters (XII) and (XIII), respectively, the reactions being smoother than those involving ethynyl ketones because of the greater stability of (III) towards alkaline reagents. Diazomethane also reacted readily with (III) in ethereal solution to yield (XIV) in good yield [its structure was not proved rigidly, and it may be the isomeric methyl 2-benzoylpyrazole-3-carboxylate. The " 3-benzoylpyrazole " obtained from diazomethane and phenyl ethynyl ketone by Bowden and Jones (*loc. cit.*) may similarly be the 2-benzoyl compound].



It was pointed out by Bowden and Jones (*loc. cit.*) that the reactions of ethynylketones in general parallel those of the hydroxymethylene derivatives of the corresponding methyl ketones, and the ethynyl ketones can often be substituted advantageously for the latter (cf. Johnson, *J.*, 1947, 346). The examples of heterocyclic syntheses given above demonstrate that $\alpha\beta$-acetylenic γ-keto-esters show a similar parallelism to $\alpha\gamma$-diketo-esters, which indeed can easily be prepared from them. Although the latter are in most cases much more readily accessible (from the condensation of oxalic ester with methyl ketones) the greater reactivity of the acetylenic compounds suggests that these may occasionally be of value.

Light-absorption data for the amine adducts described are given in Table I, the values for the nearest available analogues in the 2-aminovinyl ketone series being given for comparison. Data for the corresponding enols are given in Table II. It is clear that in alcoholic solutions these compounds exist, at any rate largely, as the vinylamine and enolic forms rather than their imino- and ketonic tautomers. The powerful auxochromic effects of the amino- and hydroxyl groups in the α-substituted β-benzoylacrylic acid derivatives correspond to those observed in the vinyl ketone series (Bowden, Braude, Jones, and Weedon, *loc. cit.*). The effect

TABLE I.

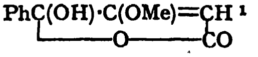
Light Absorption of Adducts.

Amino-keto-acid derivative.			Corresponding amino-ketone.[1]		
	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
$PhCO{\cdot}CH{=}C(NH_2){\cdot}CO_2Me$	2590	4,500	$PhCO{\cdot}CH{=}CH{\cdot}NH_2$ (m. p. 70°)	2420	14,000
	3520	17,000		3240	22,000
$PhCO{\cdot}CH{=}C(NH_2){\cdot}CO{\cdot}NH_2$	2460	7,000	$PhCO{\cdot}CH{=}CH{\cdot}NH_2$ (m. p. 90—91°)	2420	11,000
	2560	7,000		3240	18,000
	3430	17,500			
$PhCO{\cdot}CH{=}C(NEt_2){\cdot}CO_2Me$	2470	10,500	$\tfrac{1}{2}(PhCO{\cdot}CH{=}CH{\cdot}NH{\cdot}CH_2)_2$	2420	11,000
	3410	22,000		2450	11,000
				3450	17,000
$PhCO{\cdot}CH{=}C(NHPh){\cdot}CO_2Me$	2400	13,000			
	3730	19,000	$PhCO{\cdot}CH{=}CH{\cdot}NHPh$	2420	17,500
				2540	17,500
$PhCO{\cdot}CH{=}C(NHPh){\cdot}CO_2H$	2400	11,000		3740	31,000
	3680	14,000			

[1] Data from Bowden, Braude, Jones, and Weedon, *loc. cit.*, and Bowden, Braude, and Jones, *J.*, 1946, 945.

TABLE II.

Light Absorption of Enols.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
$PhCO{\cdot}CH{=}C(OH){\cdot}CO_2Me$	3110	15,000	cf. $PhCO{\cdot}CH{=}CH{\cdot}CO_2Me$(*cis*) [1]	2510	12,000
$PhCO{\cdot}CH{=}C(OH){\cdot}CO_2H$	3115	12,500	$PhCO{\cdot}CH{=}CH{\cdot}CO_2Me$(*trans*) [1]	2350	12,000
	3340 *	9,500		2680	9,000
$PhCO{\cdot}CH{=}C(OH){\cdot}CO{\cdot}NH_2$	2230	6,000	 $PhC(OH){\cdot}C(OMe){=}CH$ [1]	2250	13,500
	3240	14,000			
$PhCO{\cdot}C(OH){=}CH{\cdot}CO_2H$	2680	13,500			

* Inflexion.

[1] Nineham and Raphael, *loc. cit.*

of the carbomethoxyl, carboxyl, or carbamyl group on the position and intensity of the absorption maximum is not profound, but it is unexpectedly variable. The differences between the light absorption of the methyl ester and the amide of α-hydroxy-β-benzoylacrylic acid, and of the acid itself, are especially interesting; normally the conversion of an acid into its ester or amide has little effect on its light absorption. In these compounds however, the adjacent carboxyl or similar group clearly can interact with the hydroxyl or amino-group, possibly by hydrogen bonding, thereby modifying the mobility of its free electron pair and hence its auxochromic effect (cf. Bowden, Braude, and Jones, *J.*, 1946, 748).

As would be expected the hydroxyl group in β-hydroxy-β-benzoylacrylic acid has little effect on the light absorption; the difference between this compound and the β-methoxy-β-benzoylacrylic acid described by Nineham and Raphael (*loc. cit.*), which exists in the cyclic form, is noteworthy.

The acetylene carbinols required for this work were prepared by the method of Heilbron, Jones, and Weedon (*J.*, 1945, 81) with numerous minor modifications; the preparation of phenylethynylcarbinol is described to exemplify these and because existing physical constants apparently refer to incompletely purified materials. The acetylenic hydroxy-acids were obtained by the method of Haynes and Jones (*loc. cit.*) except that the Grignard complexes were prepared without heating (cf. Jones and Whiting, *J.*, 1949, 1423). It was found that with this modification and using ether as solvent, the method could be applied to phenylethynylcarbinol, contrary to previous experience; but when it was applied to propenylethynylcarbinol the syrupy product, though obtained in good yield and light in colour, was shown by its light absorption to contain about 50% of the rearranged isomer, from which it could not be separated. The method of carboxylating phenylethynylcarbinol described by Nineham and Raphael (*loc. cit.*) gave in our hands very variable results, apparently because of the unpredictable physical state of the precipitated sodium derivative; it could not be applied to propylethynylcarbinol. An attempt to carboxylate the dipotassium derivative of phenylethynylcarbinol, prepared by treating the carbinol with the potassium hydroxide–butyraldehyde diethyl acetal complex according to the method of Weizmann (B.PP. 573,527; 580,921; see also Bergmann, "Chemistry of Acetylenic Compounds," p. 50) also failed, the isolation of a small amount of acetylenedicarboxylic ester suggesting fission of the carbinol under these conditions.

EXPERIMENTAL.

(Light-absorption determinations were carried out in alcohol solutions on a Hilger medium spectrograph).

Phenylethynylcarbinol.—The apparatus consisted of a three-necked, 10-l. flask fitted with an efficient stirrer (without mercury seal) and a gas inlet tube of at least 12 mm. diameter, the whole being well insulated by immersion in cork dust. To liquid ammonia (6 l.), powdered ferric nitrate (3 g.) and sodium (10 g.) were added, and after a short interval more sodium (290 g.; ½-inch cubes). When after 20—60 minutes the colour had changed from dark blue to grey, acetylene was passed in rapidly; after some hours the colour again changed, becoming clear and black. The flow of acetylene was replaced by a slow current of nitrogen and a solution of benzaldehyde (1230 g.) in dry ether (1 l.) was added during two hours. After the flask contents had been stirred for 16 hours, ether (1·5 l.) was added, and the mixture was warmed until the greater part of the ammonia had evaporated. Ice and 6N-sulphuric acid in excess were added, and the aqueous layer was extracted with ether, the extract then being washed with sodium hydrogen carbonate and dried. After the removal of ether distillation of the residue at 0·3 mm. gave a number of fractions. The forerun (*ca.* 200 g.) b. p. 35—70°, consisted mainly of benzaldehyde and was discarded; fractions, b. p. 70—100°, consisting principally of the acetylenic carbinol were then obtained. Of these the middle portion had m. p. *ca.* 25—26° and was accepted; earlier and later fractions, the former containing much benzaldehyde and benzyl alcohol and the latter benzoic acid, were combined, dissolved in ether, and washed with saturated sodium hydrogen sulphite solution (the precipitated benzaldehyde addition compound being removed by filtration) and thoroughly with sodium carbonate solution. After the ethereal solution had been dried and the solvent removed the residue was distilled, fractions having m. p. 25—27° being retained; the total yield was 875 g. A specimen recovered from an attempted carboxylation by the method of Nineham and Raphael (*loc. cit.*) was free from benzaldehyde and had b. p. 94°/0·7 mm., n_{D}^{20} 1·5518 (supercooled), m. p. 27·5°. After crystallisation from ether–light petroleum at *ca.* −40° it formed small prisms, m. p. 28·5°, unchanged on recrystallisation from the same solvent (Jones and McCombie, *J.*, 1942, 733, give m. p. 22°; earlier workers describe this compound as a liquid).*

In the preparation of ethynylcarbinols it has been found possible to dispense with the use of a cooling bath and control of the reaction temperature. Rigorous exclusion of water by means of a mercury-sealed stirrer, soda-lime tubes, etc., is difficult and indeed somewhat hazardous because of the risk of a blockage in the latter. It is, however, preferable to decompose the sodio-complex with ammonium chloride as described by Heilbron, Jones, and Weedon (*loc. cit.*) when the carbinol is sensitive to acids or to oxidation.

3-*Hydroxy*-3-*phenylprop*-1-*yne*-1-*carboxylic Acid* (I).—Phenylethynylcarbinol (58 g.) was added during three hours to an ethereal solution of ethylmagnesium bromide [from magnesium (25 g.)], with efficient stirring and ice-cooling. The colloidal suspension obtained was stirred at 0° for a further thirty

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[*] Cf. Clapperton and McGreger, *J. Amer. Chem. Soc.*, 1949, 71, 3234.

minutes and then poured on to an excess of solid carbon dioxide in an autoclave, which was then sealed. After 22 hours the Grignard complex was decomposed, and isolation of the acidic fraction gave a dark semi-solid mass (*ca.* 70 g.). Trituration with cold benzene gave the hydroxy-acid (48·5 g.), m. p. 84—85°, which after repeated crystallisation from benzene had m. p. 89—90° (Nineham and Raphael, *loc. cit.*, give m. p. 94—95°). Conversion into the methyl ester by refluxing a methanolic sulphuric acid solution followed by distillation at 0·01 mm. (b. p. 143°) gave yields of only 45—55%, and it was found more economical to esterify the crude acid, m. p. *ca.* 84°, with cold methanolic sulphuric acid for one week, and to oxidise the undistilled ester, obtained in 85% yield, directly to methyl β-benzoylpropiolate (II) by Nineham and Raphael's method (*loc. cit.*), the yield of pure keto-ester from the crude acid then being 55%.

Hydrogenation of Methyl β-Benzoylpropiolate.—When the keto-ester (1·1 g.) was shaken with hydrogen in methyl acetate solution in the presence of a palladium–calcium carbonate catalyst until absorption was complete (uptake 240 c.c. at 769 mm. and 18°) and the product was hydrolysed with excess of aqueous–methanolic potassium hydroxide solution for 60 hours at room temperature, isolation of the acid fraction gave β-benzoylpropionic acid (0·7 g.) as colourless plates, m. p. 114° undepressed on admixture with an authentic specimen (Somerville and Allen, *Org. Synth.*, 1933, **13**, 12, give m. p. 116°).

Methyl β-Butyrylpropiolate.—To a solution of methyl 3-hydroxyhex-1-yne-1-carboxylate (Haynes and Jones, *loc. cit.*) (5 g.) in acetone (20 c.c.) a solution of 6N-chromic acid [12 c.c.; the solution was prepared from chromic acid (100 g.), sulphuric acid (160 g.), and water (500 c.c.)] was added dropwise over a period of 20 minutes with stirring, the temperature being kept below 30° by cooling in water. The solution was stirred for a further 30 minutes and water (30 c.c.) was added; isolation of the neutral fraction with ether followed by careful fractional distillation gave the *keto*-ester (2·2 g.), b. p. 43—44°/0·02 mm., n_D^{19} 1·4511 (Found: C, 62·1; H, 6·35. $C_8H_{10}O_3$ requires C, 62·3; H, 6·55%), and recovered hydroxy-ester (1·2 g.), b. p. 72°/0·01 mm., n_D^{20} 1·4595. The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in yellow needles, m. p. 77—78° (Found: C, 50·25; H, 4·1. $C_{14}H_{14}O_6N_4$ requires C, 50·4; H, 4·2%).

Methyl 3-Hydroxybut-1-yne-1-carboxylate.—The crude hydroxy-acid (Haynes and Jones, *loc. cit.*) (38 g.) was esterified with methanolic sulphuric acid, giving the *ester* (27 g.), b. p. 60°/0·03 mm., 114°/12 mm., $n_D^{20\cdot5}$ 1·4579 (Found: C, 56·15; H, 6·3. $C_6H_8O_3$ requires C, 56·25; H, 6·3%).

Methyl β-Acetylpropiolate.—A solution of methyl 3-hydroxybut-1-yne-1-carboxylate (10 g.) in acetone (50 c.c.) was treated with 6N-chromic acid solution (30 c.c.) as previously described. Isolation of the product with ether, and fractional distillation gave the *keto*-ester (6·0 g.), b. p. 79°/16 mm., n_D^{20} 1·4470 (Found: C, 56·95; H, 4·6. $C_6H_6O_3$ requires C, 57·15; H, 4·8%). The 2 : 4-*dinitrophenylhydrazone* formed yellow prisms, m. p. 166°, from ethyl acetate–ethanol (Found: C, 47·75; H, 3·55. $C_{12}H_{10}O_6N_4$ requires C, 47·05; H, 3·3%).

Hydrogenation. The keto-ester (1·2 g.) in methyl acetate (20 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (100 mg.; 2%) until absorption was complete (uptake 395 c.c.). After removal of the catalyst and evaporation of the solvent distillation gave methyl lævulate (1·0 g.), b. p. 83—85°/18 mm., n_D^{23} 1·4234 (Cowley and Schuette, *J. Amer. Chem. Soc.*, 1931, **53**, 3485, give b. p. 197·7°, n_D^{20} 1·4223). The 2 : 4-dinitrophenylhydrazone formed yellow needles, m. p. 140°, from ethanol (Cowley and Schuette, *loc. cit.*, give m. p. 141—142°).

Methyl 5-Ketohex-3-en-1-yne-1-carboxylate.—A solution of methyl 5-hydroxyhex-3-en-1-yne-1-carboxylate (4 g.) (Haynes and Jones, *loc. cit.*) in acetone (30 c.c.) was treated with 6N-chromic acid (10 c.c.) at 10°. Isolation with ether and distillation gave the *keto*-ester (1·8 g.), b. p. 67°/10⁻² mm., n_D^{20} 1·5140 (Found: C, 62·6; H, 5·1. $C_8H_8O_3$ requires C, 63·15; H, 5·3%). Light absorption (in alcohol): Maxima, 2600 and 2680 A.; ε = 15,000. The 2 : 4-*dinitrophenylhydrazone* formed red prisms, m. p. 185—186° (decomp.), from ethyl acetate (Found: C, 50·45; H, 3·75. $C_{14}H_{12}O_6N_4$ requires C, 50·6; H, 3·65%).

β-Hydroxy-β-benzoylacrylic Acid (IV).—6N-Chromic acid (11 c.c.) was added during 20 minutes to a solution of 3-hydroxy-3-phenylprop-1-yne-1-carboxylic acid (5 g.) in acetone (30 c.c.), the temperature being kept at 5—10°. After being stirred for a further 10 minutes the solution was diluted with water and extracted with ether, and the extract was washed with water, dried, and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave the *acid* as plates, m. p. 54° (Found: C, 62·45; H, 3·8. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%). It gave a crimson ferric chloride coloration. The *quinoxaline* derivative was readily obtained by mixing ethereal solution of the acid and *o*-phenylenediamine; it formed golden-yellow plates, m. p. 262°, from methanol (Found: C, 72·85; H, 4·6. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·55%). Light absorption: Maxima at 2670, 4130, and 4350 A.; ε = 12,500, 30,000, and 27,500, respectively.

β-Hydroxy-β-acetylacrylic Acid.—Oxidation of 3-hydroxybut-1-yne-1-carboxylic acid (0·8 g.) in acetone (10 c.c.) with 6N-chromic acid (3 c.c.) at 15° followed by isolation with ether gave the crude enolic *acid* (0·5 g.) as a syrup which gave an intense crimson coloration with ferric chloride solution. It was characterised as its *quinoxaline* derivative which formed brownish prisms, m. p. 248—250°, from ethanol (Found: C, 65·8; H, 5·65. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0%). Light absorption: Maxima, 2230, 2280, 2680, and 3910 A.: ε = 30,500, 26,500, 7,000, and 17,500, respectively.

α-Hydroxy-β-benzoylacrylic Acid (*Benzoylpyruvic Acid*) (VI).—A solution of methyl β-benzoylpropiolate (0·5 g.) and potassium hydroxide (0·5 g.) in aqueous methanol was set aside at 20° for 18 hours. After dilution with water and ether extraction acidification of the aqueous phase precipitated an oil which solidified during 2 days at 0°, and was recrystallised from benzene to give the acrylic acid (0·15 g.) as plates, m. p. 151° (decomp.) (Brömme and Claisen, *Ber.*, 1888, **21**, 1132, give m. p. 156—158°).

Methyl α-Anilino-β-benzoylacrylate (VII).—Aniline (400 mg.) was added to a solution of methyl β-benzoylpropiolate (400 mg.) in dry ether (15 c.c.). After 20 hours the solution was filtered to remove a small quantity of flocculent matter and the ether was evaporated under reduced pressure. The residual oil solidified and was crystallised from aqueous methanol to give the *anilino*-ester (508 mg., 85%) as glistening golden-yellow needles, m. p. 59°, unchanged on recrystallisation from the same solvent or light petroleum (b. p. 40—60°) (Found: C, 72·8; H, 5·5. $C_{17}H_{15}O_3N$ requires C, 72·55; H, 5·4%).

Alkaline hydrolysis. A solution of the ester (0·3 g.) and potassium hydroxide (0·2 g.) in aqueous methanol was set aside at 20° for 12 hours. Isolation of the acid fraction gave α-anilino-β-benzoylacrylic acid (VIII) (0·2 g.) as yellow needles, m. p. 164° (decomp.) [Brömme and Claisen, *loc. cit.*, give m. p. 168—170° (decomp.)].

The anilino-acid and the ester were readily hydrolysed by dilute mineral acid to the corresponding enols. A solution of the ester (100 mg.) in methanol (3 c.c.) was treated with 2N-hydrochloric acid (1 c.c.) at toom temperature; the progress of the reaction was shown by the disappearance of the yellow colour. After 25 minutes water was added till a turbidity just formed; on storage methyl α-hydroxy-β-benzoylacrylate (V) (61 mg.) separated as cream, fine needles, m. p. 60°, unchanged on crystallisation from light petroleum (b. p. 40—60°) (Perkin, *J.*, 1872, **25**, 833, gives m. p. 61°; Drude, *Ber.*, 1897, **30**, 955, gives m. p. 62°).

Treatment of a solution of the anilino-acid (0·5 g.) in dioxan (15 c.c.) with 2N-sulphuric acid (8 c.c.) for 20 hours at room temperature gave, after dilution with water, α-hydroxy-β-benzoylacrylic acid (VI) (0·29 g.) which after crystallisation from benzene had m. p. 154° (decomp.), undepressed on admixture with a specimen prepared as above.

Methyl α-Diethylamino-β-benzoylacrylate.—Diethylamine (1 g.) was added to a solution of methyl β-benzoylpropiolate (1 g.) in methanol–ether (5 c.c.). After 20 hours at 20° evaporation of the solvent and distillation at 85° (bath temp.)/10^{-4} mm. gave the *amino*-ester (0·8 g.), n_D^{18} 1·6060 (Found: 69·05; H, 7·05. $C_{15}H_{17}O_3N$ requires C, 69·0; H, 7·35%).

Hydrolysis. The amino-ester (0·3 g.) in dioxan (15 c.c.) was treated with a solution of potassium hydroxide (5 c.c.; 0·4 N) at 20° for 20 hours. Acidification followed by isolation with ether gave an oil (0·2 g.) which solidified when kept, and was crystallised from benzene to give α-hydroxy-β-benzoylacrylic acid (VI) (0·1 g.), m. p. 156° (decomp.) undepressed on admixture with a specimen prepared as above. It is not known whether the amino-residue was removed in the alkaline hydrolysis or whether the amino-acid is so labile towards acid hydrolysis that this occurred almost immediately on acidifying the alkaline solution.

Methyl α-Amino-β-benzoylacrylate (IX).—To a solution of methyl β-benzoylpropiolate (2·0 g.) in methanol (10 c.c.) and ether (6 c.c.) ammonia (0·8 c.c.; *d* 0·88) was added. The temperature of the mixture rose quickly to 40°, then began to fall. At this point, after about 2 minutes, the reaction was stopped by the rapid removal of all volatile material under reduced pressure. Distillation of the residue at 50—70° (bath temp.)/10^{-4} mm. gave a viscous yellow oil (1·1 g.) which partly solidified after several weeks. Recrystallisation from aqueous methanol gave the *amino*-ester as large prisms, m. p. 40° (Found: C, 64·6; H, 5·25. $C_{11}H_{11}O_3N$ requires C, 64·35; H, 5·4%).

α-Amino-β-benzoylacrylamide (X).—Ammonia (2 c.c.; *d* 0·88) was added to a solution of methyl β-benzoylpropiolate (400 mg.) in methanol (6 c.c.). After 18 hours at 20° dilution with water gave the *amino-amide* (270 mg.) which after recrystallisation from benzene formed straw-coloured needles, m. p. 137° (Found: C, 63·5; H, 5·6. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3%). It crystallised well from aqueous methanol, but then retained water tenaciously and gave inaccurate analytical data.

Both the ester and the amide were readily hydrolysed by mineral acids to the corresponding enols. A solution of methyl β-benzoylpropiolate (200 mg.) in methanol (3 c.c.) was treated with ammonia (0·5 c.c.; *d* 0·88). The solution of the amino-ester obtained by allowing the reaction to continue for 15 minutes was acidified with 2N-sulphuric acid. Next morning the separated solid was recrystallised twice from aqueous methanol, giving methyl α-hydroxy-β-benzoylacrylate (V) as long needles, m. p. 59—60° undepressed on admixture with a specimen prepared as described above. Similarly α-amino-β-benzoylacrylamide (150 mg.), dissolved in methanol (6 c.c.) and 2N-sulphuric acid (2 ml.), gave, after 30 minutes at 20°, a crystalline precipitate of α-hydroxy-β-benzoylacrylamide (XI) which after recrystallisation from aqueous methanol formed pale cream needles, m. p. 140° strongly depressed on admixture with the starting material (Found: C, 62·85; H, 4·7; N, 7·2. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·75; N, 7·35%) [Mumm and Münchmeyer, *Ber.*, 1910, **43**, 3342, give m. p. 138° (decomp.)].

Methyl 3-Phenylpyrazole-5-carboxylate (XII).—A solution of hydrazine hydrate (0·1 g.) in methanol (2 c.c.) was added slowly to a solution of methyl β-benzoylpropiolate (0·5 g.) in methanol with ice-cooling. After dilution of the solution with water and isolation with ether the methyl ester was obtained, which after crystallisation from aqueous methanol formed prisms, m. p. 177—178° (Found: C, 65·4; H, 5·45. Calc. for $C_{11}H_{10}O_2N_2$: C, 65·35; H, 5·0%) (Buchner and Lehmann, *Ber.*, 1902, **35**, 35, give m. p. 181—182°).

*Methyl 5-Phenyl*iso*oxazole-3-carboxylate* (XIII).—A solution of hydroxylamine hydrochloride (0·5 g.) in methanol (5 c.c.) was neutralised with methanolic sodium methoxide (5 c.c.) and filtered from precipitated sodium chloride. A portion (8 c.c.) of the resultant solution was added to methyl β-benzoylpropiolate (0·5 g.) in methanol (5 c.c.), and the mixture was set aside for 18 hours at 20°. Isolation with ether then gave the *ester* (0·15 g.) as plates, m. p. 86—88° (Found: N, 6·65. $C_{11}H_9O_3N$ requires N, 6·9%).

Methyl 3(4?)-*Benzoylpyrazole*-4(3?)-*carboxylate* (XIV).—A solution of methyl β-benzoylpropiolate (1·0 g.) in ether (5 c.c.) was treated with an excess of ethereal diazomethane. After 18 hours at 20° evaporation of the solvent and crystallisation from aqueous methanol gave the *ester* as well-formed prisms, m. p. 138° (Found: C, 62·7; H, 4·6. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4%).

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Imperial College of Science and Technology, London, S.W.7.
The University, Manchester, 13.

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56. *Heterogeneous Catalysis. Part I. Theoretical Basis.**

By D. A. Dowden.

In heterogeneous catalysis the rate of reaction is controlled by the formation of a chemisorbed complex which may be bound to the solid surface by ionic or covalent bonds.

If the rate is limited by the formation of a positive ion at a metal surface, the process is most favoured and fastest when the ionisation potential of the metal atom and the metal work function are both large, and when the gradient of electron level density with electron energy at the Fermi surface is large and positive. Formation of negative ions is optimum with small metal ionisation potentials and work functions but with an electron level density gradient which is large and negative.

Covalent bonding is treated qualitatively using Pauling's newer concept of transitional metal valencies, and the electron band theory, with the result that bonding appears most favoured and fastest on metals possessing vacant " atomic " *d*-orbitals, or a large density of electron levels close to the Fermi surface.

Activity in multiple-bond hydrogenation is associated with the " holes " in transitional metal *d*-bands, and falls to a very low value at those alloy or inter-metallic compound compositions where the " holes " are just full. These principles are applied to many catalytic phenomena, *e.g.*, poisoning.

Analogous ideas are applied to semi-conducting catalysts where activity is associated with the electron levels and lattice defects arising from impurity centres or non-stoicheiometry.

It is suggested that insulator catalysts, *e.g.*, γ-Al_2O_3, function through a proton-exchange mechanism which is particularly easy at cation defects.

1. INTRODUCTION.

WAR-TIME exigencies in industry yielded a variety of novel catalysts selected almost wholly by empirical methods and revealed our almost total ignorance of the precise rôle of the solid in heterogeneous catalysis.

In 1943 a survey of the relevant literature, including patents, showed either a complexity wherein one could not " see the wood for the trees " or kinetic studies for the most part uncorrelated with the electronic and geometric characteristics of the catalyst lattice. Separate small researches with limited objectives gave a pattern of results, broadly interpretable according to the " active centre " concept and its several models, but not at that time picturing details of importance for industrial catalyst design.

With the advent of the quantum theory of the covalent bond and transition state treatment of the activated complex, the active centre came to be portrayed as one surface atom, or a group of such atoms, possessing a unique configuration and orientation relative to certain substrate parameters. As long as such a centre could be represented by a portion of a normal lattice plane, the model was useful, but when special nuclei were postulated, having properties not simply related to those of the catalyst crystallite bulk, its heuristic value was severely limited.

Chemisorption of one or more of the reactants at an active region appeared as the first requisite of a solid catalyst in any heterogeneous reaction, chemisorption of the activated complex of the rate-controlling step determining the overall reaction rate. The bonding of the chemisorbed species with the surface might be, in the extreme, ionic or covalent.

A re-assessment of the catalytic problem then falls naturally into three parts: (*a*) a description of the chemisorbed particles, (*b*) a description of the active regions, and (*c*) the interactions in the group of particles plus regions.

The kinetics of homogeneous catalysis have been considerably advanced in recent years by the introduction of entities such as the free radical and the radical ions, and by the use of the Lewis viewpoint on generalised acid–base catalysis. Broad analogies, drawn between homogeneous acid-catalysed reactions and similar heterogeneous processes at the surface of some cation-defective oxide insulators containing protons, encourage the view that the same intermediate particles are active in both. Less well-defined relations suggest identical species at the surface of metals and semi-conductors (Bremner, *Research*, 1948, **1**, 281).

The electron shifts resulting in radical and ion formation reveal the catalyst crystallite as an electron source or sink and, in the presence of hydrogen-containing materials, as a potential proton reservoir. Lennard-Jones (*Trans. Faraday Soc.*, 1932, **28**, 333), Schmidt (*Chem. Reviews*, 1933, **12**, 363), and Nyrop (" The Catalytic Action of Surfaces," London, 1937) were aware of some of the implications of the former rôle. The binding electrons will be found in electronic levels and the chemisorbed particles in geometric sites which together minimise the free energy of activation and make the overall free-energy change a maximum for the bonding process.

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* Presented, in substance, at a Chemical Society Discussion, London, on March 17th, 1949.

The electron-band concept of solids and the classical ionic-lattice theory, together, provide a reasonably adequate qualitative description of the significant electron and ion energy levels in the principal solid types while detailed application of conventional physical techniques to crystals and glasses has rapidly increased the number of known macroscopic and microscopic lattice defects.

It seemed therefore in 1943 that a definite correlation must exist between the electronic structure of solids and their catalytic activity; in fact a number of useful working rules were derived. Unfortunately it was not possible to commence experiments directed to the verification of these until 1946 (the data in the literature were equivocal). Recent publications concerning the catalytic activity of pure metals and alloys in hydrogenation and dehydrogenation reactions, and related observations on the catalytic, adsorptive, etc., properties of pure and so-called " mixed " oxides, imply a growing awareness of such relations. A partial statement of the situation has been published by Schwab (*Trans. Faraday Soc.*, 1946, **42**, 689) and Garner (*J.*, 1947, 1239).

This paper describes some present ideas on the subject as an interim report on a unitary theory of catalysis (Dowden, *Research*, 1948, **1**, 239).

2. The Geometry of the Catalyst Particle.

All bulk catalysts are aggregates of an entity which is taken to be a crystallite in normally crystalline materials (*e.g.*, metals) but a glassy or gel-like particle in amorphous catalysts derived from glass-forming constituents. These ultimate particles are the units affecting catalysis and possess, it is assumed, the following additional characteristics : (i) The volume properties and the surface properties (per unit surface) are identical with those of the massive material. (ii) Defective and ordered or disordered states, when present in the virgin catalyst lattice, exist unmodified right up to the solid–gas interface unless tending to equilibrate with the gas phase. (iii) Single-phase multicomponent catalysts, macroscopically homogeneous, have no excess or deficiency of any component in the surface at equilibrium. Thus, in an equilibrium copper–nickel solid solution, there is no copper enrichment at the surface. (iv) The particles are bounded by essentially plane surfaces.

It should be noted that (i) probably fails below some small particle size while (ii) may not be exactly true even at equilibrium in view of the asymmetry at the surface.

At temperatures above absolute zero, in addition to vibratory heat motion, a small fraction of the lattice ions are displaced from their lattice positions to yield Frenkel and Schottky defects (see section 10). Catalysts prepared below the Tammann temperature ($\frac{1}{2}$ × m. p. in °K.) may have a concentration of such defects considerably in excess of the equilibrium value.

3. Specific Area of the Solid.

The catalysed reaction proceeds at a gas–solid interface so that its rate must be a direct function of the specific area (area per unit weight) of the catalyst. Diffusion may limit effective reaction to a fraction of the total surface, but if the available area remains proportional to the total then activity per unit catalyst weight is proportional to specific area; this has been demonstrated experimentally (*e.g.*, Siller, *J. Amer. Chem. Soc.*, 1943, **65**, 431).

Catalyst modification can alter both specific area and activity per unit area (specific activity), and the two must be evaluated separately. The factors controlling development or maintenance of a given specific area are usually less critical and better known than those affecting specific activity; they will not be discussed further.

4. Specific Activity.

Activity per unit area, a function of catalyst composition and state, is independent of specific area within the approximations of section 2.

When the system is chosen so that volume and surface diffusion steps are very fast a catalytic reaction can be formally presented as (i) chemisorption of one or more reactants, (ii) reactions in the total adsorbate plus surface complex, and (iii) desorption of the products.

In the stationary state the overall reaction rate (V_s) is that of the slowest step.

$$V_s = k \times (A)^m \times (B)^n \times \ldots\ldots \qquad (1)$$

where letters in parentheses represent surface or volume concentrations of those species yielding the activated complex.

The rate constant k equals

$$K\frac{kT}{h}\exp.\left[-\Delta F^{*}/kT\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

or

$$K\frac{kT}{h}\exp.\left[-\Delta U^{*}/kT+\Delta S^{*}/kT\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

K is the transmission coefficient, ΔF^{*}, ΔU^{*}, ΔS^{*} are the Helmholtz free energy, intrinsic energy, and entropy of formation, respectively, of the complex. k is the Boltzmann constant and h is Planck's constant.

Ideally the reaction mechanism can be defined and ΔF^{*} evaluated at the slowest step. In practice the trends in ΔF^{*} at the likely controlling steps must be predicted from semi-empirical rules.

(a) *Chemisorption.*—When adsorption or desorption is the limiting process the Lennard-Jones (*loc. cit.*) free-energy diagram illustrating activated adsorption is informative (see Fig. 1, where only electronic entropy contributions are included).

FIG. 1.

Free energy changes in the sorbed state. Only electronic entropy changes included. Positive ion formation.

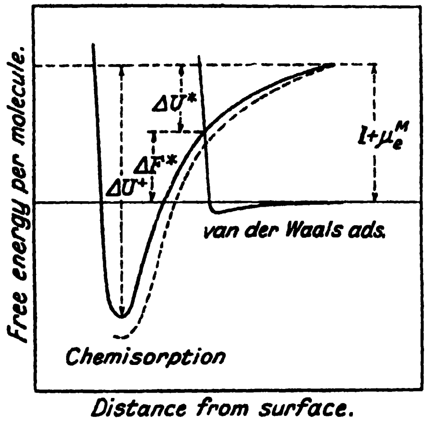
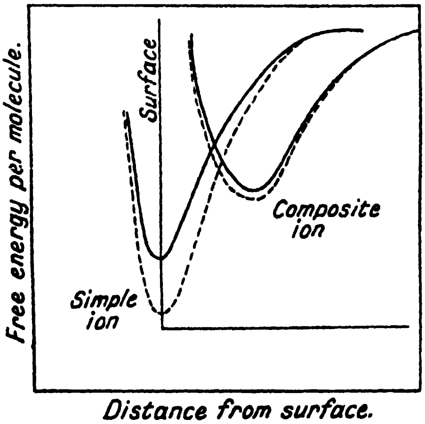


FIG. 2.

Free energy changes for a reaction in the adsorbed state.



The van der Waals adsorption free energies of a substrate are generally small, their differences still less at similar sites on a series of catalyst surfaces, so that the free energy of activation depends chiefly on the contour of the chemisorption curve, the value of the chemisorption free energy, and the distance between the two minima. On catalysts of the same solid type, if the change in force law is small, ΔF^{*} decreases as the chemisorption free energy increases or when the distance between the equilibrium van der Waals and chemisorption positions diminishes. Active centres must therefore be associated with adsorption sites, the geometry of which requires the minimum movement of the mass centre of the particle during the transition, consistent with a maximum chemisorption free energy. Desorption free energy of activation, being the sum of ΔF^{*} and the chemisorption free energy, can be made smaller only by modifications simultaneously minimising both the chemisorption free energy and the distance between equilibrium positions. These conclusions are independent of the nature of the bond with the surface (cf. Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, 31, 1375).

(b) *Reactions in the Adsorbate.*—Generalisation is more difficult when reaction between adsorbed species provides the rate-controlling step, as the participants may be molecules, radicals, or ions. Nevertheless a sufficiently detailed analysis of a reaction mechanism usually reveals a unimolecular or bimolecular process as the slowest step. For example :

$$\mathrm{ROH} + \mathrm{H}^{+} \longrightarrow \mathrm{ROH_2}^{+}$$

or

$$\mathrm{ROH_2}^{+} \longrightarrow \mathrm{R}^{+} + \mathrm{H_2O}$$

or

$$\mathrm{R}^{+} \longrightarrow \text{Olefin} + \mathrm{H}^{+}$$

Where the neutral molecules are physically adsorbed, the ions are held by Coulomb forces, and each ion is partitioned between the surface and a neutral molecule at the surface (Fig. 2).

Arguments, similar to those of section (*a*), suggest that the activation free energy will be lowered as the equilibrium positions are brought closer together. Catalyst changes must move the curves in the same direction parallel to the ordinate, when the forces are purely ionic and the ions of one sign, but, the radius of the composite ion being greater, the changes will there be less than for the simple ion of smaller radius (the small ion is more correctly taken to be embedded in the catalyst surface). According to this model therefore, the activation free energies for composite or simple ion formation are lowered by decreasing or increasing, respectively, the adsorption free energy of the simple ion; active centres can be defined as sites which minimise the separation of the ions and change the adsorption free energy of the smaller ion to its lowest or highest level.

When the intermediates are adsorbed radicals (as possibly at metal surfaces), the situation can be described similarly, but free energy changes cannot be easily discussed even on simple bases.

In subsequent sections consideration will be given to those factors affecting the free energy and geometry of adsorption, since these are paramount in predicting activity trends over " homologous " series of catalysts.

5. ELECTRON TRANSFER AT SURFACES.

Recent studies of the electrical properties of solid–fluid interfaces emphasise the existence of electron-transfer and exchange phenomena between surface and sorbate, whereby neutral molecules can yield one or more adsorbed ions (positive and negative) or radicals, depending on the electronegativities of the surface and the molecular fragments (Seitz, *J. Appl. Physics*, 1937, 8, 246).

Spontaneous production of a surface dipole on adsorption happens when a normally full electron level lies above a normally empty level. If the donating level lies below the acceptor level then an activation energy is required.

There are at least five pre-requisites of electron-transfer changes:

(i) The free energy change of the overall process must be negative.

(ii) At the position of van der Waals adsorption the normally full substrate levels (minimum ionisation potential I) or empty levels (maximum electron affinity E) must be brought close to the normally empty or full levels, respectively, of the catalyst crystallite.

(iii) Either (*a*) the discrete electron levels of the isolated sorbate species must broaden as the surface is approached so that the minimum ionisation potential of the sorbate is decreased and its maximum electron affinity increased, or (*b*) the levels may remain discrete even at the surface, but I and E change as in (*a*).

(iv) The catalyst crystallite must possess vacant or occupied levels capable of accepting or donating electrons to form the activated complex [another aspect of (ii)].

(v) The potential barrier separating the crystal levels and the sorbate levels, when it exists, must be permeable to electrons.

Level broadening occurs when I and E are less that the inner potential of the crystal, providing that the corresponding levels interact with a quasi-continuous band of levels in the solid.

The inner potentials of metals range from 7·3 ev. (K) to 16 ev. (Ni) and seem to fall, as far as they have been measured, between 12 ev. and 16 ev. midway in a long period (Fowler, " Statistical Mechanics," 2nd Edn., Cambridge, 1936, p. 355). In semi-conductors and insulators similar magnitudes appear (O'Bryan and Skinner, *Proc. Roy. Soc.*, 1940, *A*, 176, 229).

Remembering that measured values of the inner potential are only average values for the crystal, and noting the effect of electrical image forces in reducing ionisation potentials, it is reasonable to assume that the inner potentials of the transitional elements, and of other compounds of catalytic interest, are always greater than the ionisation potentials of normal sorbates.

In typical metals the volume electron levels lying above the inner potential are always quasi-continuous, except for narrow forbidden regions confined to certain directions in some lattices, *e.g.*, those of bivalent metals. Insulators differ in having a wide region of forbidden energy levels lying between the top of the full band and the bottom of the empty band; sorbate levels cannot interact with this forbidden region. Semi-conductors have more or less localised and discrete, full or empty levels in this energy gap. Interaction between sorbate levels and these semi-conductor levels depends on the energy, and density in energy and volume of the latter.

Juxtaposition of the relevant levels, according to (ii), is exact when the radius, ionisation potential, and electron affinity of the adsorbed particle are equal to those of a lattice atom or ion. In saturated molecules the first two characteristics are larger, and the third smaller than those of metal atoms, so that the required adjustment of levels can occur, if at all, only in special positions. Analogous remarks can be made of ionic lattices.

At absolute zero the energy levels of a metal crystal are full up to the Fermi surface of energy $-\phi$ (ϕ = metal electron work function). All levels above this are empty but above 0° K. the cut-off becomes diffuse due to thermal energy. Both vacant and full levels may correspond to eigen-functions of *s*, *p*, *d*, or mixed character.

Bound surface states of various origin may exist. These comprise levels corresponding to crossing of atomic levels (Shockley, *Phys. Review*, 1939, **56**, 317), to variation in Madelung potential at the surface (Mott, " Electronic Processes in Ionic Crystals," Oxford, 1940, p. 86), and to the presence of the sorbate (Lennard-Jones, *loc. cit.*; Pollard, *Phys. Review*, 1939, **56**, 324). Such states lying above the Fermi surface will be empty, those lying below will be full and in metals, because of transitions between the surface and volume levels, need not be considered in detail. In semi-conductors and insulators, on the other hand, surface levels where they arise may be of considerable interest.

FIG. 3.

Energy of an electron in the potential field of the metal and the substrate positive ion.

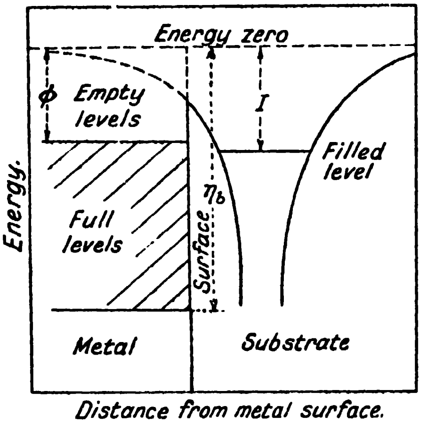
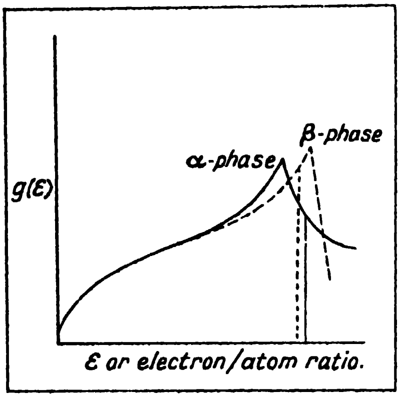


FIG. 4.

Electron level density in Hume-Rothery alloys.



Now that the general conditions leading to electron movement have been sketched, some special cases will be treated for various solid types on the assumption that the above conditions hold.

6. METALS.

In metal crystals the lattice electron affinity equals the lattice ionisation potential and the electron exit work function.

(i) *Positive-ion Formation.*—Positive ions are formed by transferring an electron from the highest occupied level ($-I$) of the absorbed species to the lowest unoccupied lattice level ($-\phi \simeq \mu_e^M$) when $I^1 \leqslant \phi$ (Fig. 3).

(a) ***Equilibrium.*** If the sorbate at the surface is considered to be a surface phase, the electrons of which are in equilibrium with those of the metal phase through a dilute electron gas, then the ratio of ionised species in the surface phase is given by

$$^0A^+/^0A = \frac{\mathrm{f}(A^+)}{\mathrm{f}(A)} \exp. [-(I^1 + \mu_e^M)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where

$$I^1 = I + \Delta U^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and

$$\mu_e^M = -\phi - 1/6\pi^2k^2T^2(\mathrm{d}\log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon=-\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

(see Fowler and Guggenheim, "Statistical Thermodynamics," Cambridge, 1939, p. 472). f(A^+) and f(A) represent partition functions for the ionised and neutral particles respectively, $\mu_e^M = (\partial F_e^N/\partial N)_v$ equals the thermodynamic potential per metal electron per unit volume, I is the ionisation potential of the neutral particle, ΔU^+ the adsorption energy of the ion (always negative, corresponding value for the neutral particle $\simeq 0$), $g(\varepsilon)$ the density in energy of electron levels per unit volume, and ε the metal electron energy.

The entropy change per added electron in the metal corresponding to μ_e^M is

$$(\partial S/\partial N)_v = 1/3\pi^2k^2T(\mathrm{d}\log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon=-\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and can be neglected as in some thermionic work except when $(\mathrm{d}\log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon=-\phi}$ is large.

The electron exit work function (ϕ) is known accurately only for a few pure metals, so that it will be useful to note that it is defined by the approximate relation

$$N \simeq \int_{-\eta_b}^{-\phi} 2g(\varepsilon)\,\mathrm{d}(\varepsilon) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

N is the number of electrons per unit volume of metal and $-\eta_b$ the energy at the bottom of the electron band.

Other things being equal, $|\phi|$ increases as $g(\varepsilon)$ increases.

The ionised electron need not enter the crystal at the Fermi energy level. For instance, in metals having holes in the *d*-band, surface atoms will have a certain lifetime in charged states corresponding to singly- or multiply-charged positive ions, and the donated electron will tend to enter one of these " ionised " levels. However, the Pauli principle ensures that this process from the equilibrium standpoint is equivalent to the addition of an electron at the Fermi level. Gurney (*Phys. Review*, 1935, **47**, 479) has indicated that the ionisation potential of the metal atom, rather than the work function of the metal crystal, is the better parameter to use in the treatment of ionisation at surfaces. ${}^0A^+/{}^0A$ is a maximum for a given sorbate when I^1 is a minimum and $|\mu_e^M|$ a maximum.

(b) *Geometry of the " active centre."* In a given system $|\Delta U^+|$ is a maximum (and I^1 a minimum) when the ion has acquired the greatest number of lattice atom nearest neighbours. In this state the ion takes up a position interstitially at the surface, or as near as possible to a vacant surface lattice point.

From another viewpoint, since level breadth increases exponentially as the distance between the absorbate and the surface atoms decreases, I will be a minimum when the neutral adsorbate is itself in equilibrium at a lattice defect.

Obviously such sites are most likely to exist on catalyst planes of least packing density, *e.g.*, (111) of α-iron and (110) of nickel, or at a point in the surface plane from which an atom is missing. At these centres minimum movement of mass centre occurs between the physically and chemisorbed states contributing to a minimum activation free energy; the values of parameters giving most favourable equilibrium give also the greatest ionisation velocity.

The continuity with older work on the relative energies of surface lattice points of various co-ordination number and with the more recent ideas of lattice dislocations is obvious (Mott and Nabarro, " The Strength of Solids," Physical Society, London, 1948, p. 1).

(c) *Rate.* The free energy of activation depends on the value of ΔU^+ for the system in the activated state. Reference to section 4(a) shows that it is a reasonable approximation to put the adsorption energy of the ionic activated complex proportional to ΔU^+, *i.e.* $\Delta U^* = a\Delta U^+$ where a is a constant <1.

Then

$$\Delta F^* \propto I + \mu_e^M - a\Delta U^+ \quad \text{or} \quad \Delta F^* = b(I + \mu_e^M - a\Delta U^+) \quad . \quad . \quad . \quad . \quad (9)$$

where b is a constant and ΔU^+ now refers to the value of the ionic adsorption energy.

The corresponding entropy of activation

$$\Delta S^* \propto T(\mathrm{d}\log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon=-\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and for k^+, the rate constant for ionisation, we have

$$k^+ = K^+ \exp.\,[-b(I^* + \mu_e^M)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where $I^* = I - a\Delta U^+$ and $K^+ =$ a transmission factor.

The value of each parameter depends on the condition of the surface, that is to say whether it is bare, in unstable condition as in the induction period, or in a stationary state.

Over a " homologous " series of metals such as a series of solid solutions, and using a given sorbate, ΔU^+, ϕ and $g(-\phi)$ vary.

(d) *Factors affecting* ΔU^+ *and* I^*. In this formal presentation, the magnitude of the ionisation potential at the surface depends wholly on ΔU^+ when the forces binding the ion are taken to be purely coulombic; ΔU^+ increases as the ion gets closer to its lattice nearest neighbours. Generally the adsorbed ion diameter (D) exceeds that of the lattice atoms (d), and ΔU^+, at a vacant lattice point or interstitially, increases with increasing d since the molecule and ion can merge more closely with the metal. If ΔU^+ varies linearly with ion-surface distance, then $\Delta U^+ \propto f(d)$, where a simple model shows that fractional changes in d (when $D > d$) produce corresponding changes in the adion equilibrium distance smaller by a factor of ~ 10. Metal atom diameters, in any long period between groups 5 and 2 (*e.g.*, vanadium through nickel to zinc), show a maximum variation between successive members of 10% and an average variation of 3%; between iron and copper the maximum variation between successive members is 3·2%, between ruthenium and silver 5·1%, and between osmium and gold 4·4%. This is also the order of the change in radius of both the vacant sites in the surface planes of greatest packing density, and the interstices in the planes of least packing density, when the lattices are of the same type. Change of crystal type causes abrupt radius differences in the interstices, such as the increase in interstice radius by *ca.* 15% at the transition from the body-centred cubic to the face-centred cubic metals (iron to cobalt, molybdenum to rhodium, tungsten to iridium), and a much larger increment when hexagonal close packing occurs (zinc, ruthenium, cadmium, rhenium, osmium). It will be assumed therefore that varying d from catalyst to catalyst has negligible effect upon ΔU^+ when the metals are near neighbours and no change in lattice type is apparent. This is particularly true of the series iron, cobalt, nickel, and copper in their face-centred cubic forms.

If the linearity between ΔU^+ and ion-surface distance in the critical range is not a good approximation, then atomic diameter in the catalyst will have a somewhat larger influence on ΔU^+ than suggested above. The purely coulombic conditions are most likely to be satisfied when the ion has an inert gas structure, and when overlap is small; generally this is not so and ΔU^+ will be augmented by exchange forces of the kind described below.

Ionisation need not be simple but may produce a number of positive ions so that I must be replaced by a quantity representing a sum of dissociation energies and ionisation potentials and ΔU^+ by a sum of adsorption energies.

(e) *The electron exit work function.* The work functions of metals and alloys are largely inaccurate or unknown, but available data indicate a trend in each long period to a flat maximum in group 8, probably at nickel, palladium, and platinum where the peak in electron level density at the Fermi surface also appears.

When ϕ is not known, as in alloy systems, it cannot be calculated since it is a sum of lattice inner potential, electron kinetic energy, and intrinsic surface dipole, none of which can be estimated to the required accuracy. Generally ϕ is greatest when $g(-\phi)$ is as large as possible, which is equivalent to taking electron kinetic energy as the dominant term in the sum. Thus in alloy systems where increasing electron to atom ratio shifts the Fermi surface to regions of smaller $g(-\phi)$, it will be assumed that the rate of decrease of ϕ is larger. Certainly the rate of increase of maximum electron kinetic energy per added electron is greatly increased in such regions, *e.g.*, at the composition where a *d*-band becomes full or where a Hume-Rothery alloy changes phase.

In a metal crystal ϕ depends upon the indices of the surface plane and changes with lattice type; lattices and faces of densest packing seem to possess work functions slightly greater than the rest by a few tenths of an electron-volt.

The positive dipole produced at the surface by the adsorbed ions reduces ϕ until the electron transfer ceases when only a fraction of the surface is covered with ions. Clearly electropositive contaminants decrease ϕ and the equilibrium surface concentration of ions as well as the rate of ion formation; electronegative species have the opposite effect.

(f) *Electron level density.* The density of electron levels at the Fermi surface, $g(-\phi)$, attains maxima in group 8 at nickel and perhaps palladium and platinum, falling to much lower values in their alloys with copper, silver, and gold respectively, at approximately the equiatomic composition. Similar rapid changes in level density occur at the phase boundaries of Hume-Rothery alloys. Again the data are not sufficiently accurate for our purposes since they provide only average value of $(\delta \log_e g(\varepsilon)/\delta\varepsilon)_{\varepsilon=-\phi}$ over fairly wide ranges of composition whereas $(d \log_e g(\varepsilon)/d\varepsilon)_{\varepsilon=-\phi}$ is required at a special composition.

A large positive value of the gradient implies an appreciable positive entropy contribution and a fall in the activation free energy; a large negative value for this parameter has the opposite effect.

While the simple band scheme provides a qualitative picture of these variables, it breaks down if pushed too far and data are too scanty to yield adequate corrections at the present time.

(g) *Change of adsorbate.* When the catalyst remains unchanged but the adsorbate varies, both I and ΔU^+ are affected. The ionisation potential of the electron removed from the adsorbate is greater or smaller depending on its bonding or non-bonding character and the environment in the molecule (Price, *Chem. Reviews*, 1947, **41**, 257). In a homologous series of molecules of increasing molecular weight, I decreases and the molecule diameter or length increases as the series is ascended. These parameters are not necessarily identical with those of the earlier considerations since in complex molecules only the smaller groupings can be accommodated at an active centre. Thus in $C_nH_{2n+1}\cdot OH$ adsorption the appropriate radius might be that of OH and the ionisation potential that of the non-bonding oxygen electrons; alternatively the radius of CH_3 or covalently-bound H, and the ionisation potential of the C–H bond, might be appropriate. When the reactant possesses non-localised electrons or electrons which can be excited to low lying non-localised orbitals, the relevant ionisation potential is that of the molecule as a whole. Evidently in large molecules ionisation can occur at one or more groups corresponding to multiple attachment to the surface with all its geometrical consequences. Whether the ionised electron is bonding or non-bonding the resulting ion is often unstable, as the results of mass spectroscopy often indicate (Hipple, Fox, and Condon, *Phys. Review*, 1946, 347).

Summarising, it appears that positive-ion formation is most favoured and fastest on metals and alloys possessing the following properties : large electron exit work function, large positive value of $(d \log_e g(\varepsilon)/d\varepsilon)$ at the Fermi surface, crystallisation such that planes of least dense packing are exposed to the gas phase or such that other more densely packed planes have a high concentration of vacant sites and controlled quantities of electronegative additives.

(ii) *Negative-ion Formation.*—A negative ion is formed by removal of an electron from the highest occupied level $-\phi \simeq \mu_e^M$ of the crystallite to the lowest unoccupied level ($-E$ = electron affinity at the surface) of the adsorbed species.

This process is the converse of that given for positive-ion formation and the fraction of ionised species in the surface phase :

$$ {}^{0}B^{-}/{}^{0}B = \frac{f(B^-)}{f(B)} \exp. [-(E' - \mu_e^M)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where

$$E' = E + \Delta U^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

E is the electron affinity of the isolated substrate and ΔU^- the adsorption energy of the anion, both being negative in the cases of interest.

The argument now runs much as before. Owing to the large polarisability of the negative ion there is a small image effect increasing the electron affinity at large distances from the surface, but the big increment comes into play only when the adsorbate approaches an active centre defined exactly as for positive-ion formation. A chief point of difference is the relatively large size of the anion which reduces the coulombic contributions to ΔU^- and suggests that only strongly electronegative particles form negative adions in the absence of overlap forces. The free energy of activation for ionisation is again

$$\Delta F^* \propto E + c\Delta U^- - \mu_e^M \text{ or } \Delta F^* = d(E + c\Delta U^- - \mu_e^M), \text{ where } c \text{ and } d = \text{constants} \quad . \quad (14)$$

and the corresponding entropy

$$\Delta S^* \propto - T(d \log_e g(\varepsilon)/d\varepsilon)_{\varepsilon = -\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

The rate constant for ionisation is

$$k^- = K^- \exp. [-d(E + c\Delta U^- - \mu_e^M)/kT] \quad . \quad . \quad . \quad . \quad . \quad (16)$$

The electron affinity E is unknown for most particles; the best values and the largest are available for oxygen, sulphur, and the halogens.

Negative-ion formation is fastest and most favoured on metals and alloys possessing the following properties : low electron exit work function, large negative value of $(d \log_e g(\varepsilon)/d\varepsilon)$ at the Fermi surface, all electronegative contaminants excluded, controlled quantities of electropositive additives.

(iii) *Covalent Bonding.*—Electron exchange affecting bonding through the resultant resonance energy yields two conveniently distinguishable bond types: the metallic bond, where the bonding electrons are more or less mobile, and the covalent bond, where they are localised between the bound atoms to give a directed bond. These and intermediate bond types can arise in chemisorption.

The ratio of the work function to the first ionisation potential is about 0·5 for most elements, and atoms of metal may be deposited from the vapour on to the metal surface to form a chemisorbed layer which is an extension of the metal crystal. In the same way atoms of zinc, phosphorus, arsenic, hydrogen, and nitrogen, having first ionisation potentials between 9 and 15 ev. form solid solutions or metallic compounds with some of iron, copper, nickel, and palladium ($\phi = 4{\cdot}5$—5 ev.). The intermediate chemisorbed state cannot differ markedly from the equivalent two-dimensional solid solution, and will possess bond character of the same kind as the bulk solution, modified by the asymmetry at the interface. Similarly a gas such as carbon monoxide forms a surface complex in which the bond approximates to that in the metal carbonyls. Morris and Selwood (*J. Amer. Chem. Soc.*, 1943, **65**, 2245) observed magnetic changes on poisoning a metallic nickel catalyst with mercury, lead, and carbon monoxide, which parallel those expected on formation of solid solutions or nickel carbonyl, and support such a correspondence. Most radicals and unsaturated molecules have ionisation potentials in the above range or smaller, and homopolar bonding is expected.

Electron exchange to cause covalent bonding occurs between levels of the catalyst–substrate complex of comparable energy; moreover, since a condition of resonance is that the extreme neutral and ionic forms must involve only small displacements of the nuclei, the geometric properties already given for an active centre are optimum here also. Other things being equal, the adsorption free energy will be proportional to the adsorption energy of the radical or molecule, *i.e.*, to the additional resonance energy of the system.

(a) *Metallic bonding.* If interactions of substrate levels with all metal levels are considered qualitatively, in a molecular-orbital approximation where the metal volume levels remain mainly unaffected, it appears that a number of electrons equal to the loosely bound (" valency ") electrons of the substrate, must be promoted to the lowest, unfilled, essentially metallic level of the complex. These anti-bonding electrons must therefore be accommodated at the Fermi surface and this will be accomplished most easily when the difference in energy between the metal work function and the substrate ionisation potential at the surface is a minimum and when the energy density of levels at the Fermi surface is large (compare a copper or zinc atom alloying with a nickel surface). A physically absorbed, large saturated molecule, at a plane surface without defects, possesses a large ionisation potential and $I - \phi \sim 10$ ev. Homopolar-bond formation on closer approach can result only when the energy gained by the depression of the bonding levels exceeds that required to put electrons in the anti-bonding levels. Interaction produces a symmetrical divergence of bonding and anti-bonding orbitals about the unperturbed substrate levels, but since the metal levels are initially full at this energy no appreciable energy can be gained, certainly not 10 ev., and no bond can be formed. Bonding on this basis is possible only for initial levels close to the Fermi surface where the anti-bonding levels may be largely empty. The process is equivalent to the elevation of a metal electron, from a filled level near the substrate level, to the Fermi surface followed by interaction between the substrate level and the now unfilled metal level (Lennard-Jones, *loc. cit.*).

By analogy with solid solution effects, chemisorption is easiest when the substrate ionisation potential is less than or equal to approximately twice the catalyst work function. The limiting ionisation potential may be smaller or larger than this when the covalent radius of curvature of the intruding electron distribution is larger or smaller respectively than that of the metal atoms. Chemisorption of saturated molecules with I greater than this limit is possible only in special positions (active centres), as already described. Dissociation of the molecule into radicals of smaller I and possibly smaller radius (*e.g.*, hydrogen atoms) is a much more likely event. Saturated molecules (*e.g.*, H_2) and " unsaturated " molecules such as carbon monoxide, carbon dioxide, nitrogen, etc., because of their small covalent radius or that of the atoms into which they may split, can merge more into the metal and behave as though of lower ionisation potential than the same molecules *in vacuo.*

If the catalyst crystallite is sufficiently large for the filling of its electron levels to remain essentially undisturbed by the chemisorption, then the addition of the anti-bonding electrons at the Fermi surface introduces an electronic entropy contribution which has the same dependence on the gradient of electron level density as given for ionic bonding.

(b) *Localised bonding.* The localised bond properties follow most simply from Pauling's recently formulated valencies for the transitional series of metals (*Phys. Review*, 1938, **54**, 899;

Proc. Roy. Soc., 1949, *A*, **196**, 343) if electron pairing in chemisorption occurs both in the unfilled "atomic" orbitals (maximum number 2·48 per atom), and in the unused fraction of surface "bonding" orbitals (maximum number 6 per atom). The number of ligands of the surface atoms is less than that for a bulk atom by a factor of $\sim \frac{1}{2}$ and the geometry is asymmetric, so that the surface orbitals need not have the same character or distribution as those in the interior. Magnetic data (Selwood, *loc. cit.*; Dilke, Eley, and Maxted, *Nature*, 1948, **161**, 804) seem to show that the "atomic" orbitals are occupied by the electrons of chemisorbed species, although what probably happens is a rehybridisation of orbitals on the surface atoms to give the strongest bond with the substrate *s*-, *sp*-, or *p*-orbitals, while maintaining maximum metal-atom-to-metal-atom cohesion. Since *dsp*-orbital strength increases with *d*-content, one may expect strong bonds to be formed most easily where almost pure *d*-orbitals ("atomic orbitals") already exist, unused in metal–metal bonds. This means that covalent-bond formation should be favoured and fast on metals with unfilled "atomic orbitals." However it does not follow that bond strength must increase with increasing number of these vacant orbitals (estimated for interior atoms), because there will be modifying surface effects and energy limitations.

Taking the localised bond and the band models together suggests that the strongest covalent bonding of a substrate would result when the density of *d*-levels is largest compared with that of the *s*-, *p*-levels at the Fermi surface. This maximum in *d*-level density occurs close to pure nickel and its congeners in the transitional series. Copper and zinc can form bonds of comparable strength only after formation of an excited state requiring considerable energy input; actual bonds in chemisorption will therefore be weak.

(c) *Surface states* (Lennard-Jones, *loc. cit.*). At sufficiently small distances between the adsorbed particle and the metal surface, the superposition of the potential well of the particle on the potential step at the metal–gas interface produces a potential well just inside the metal, the depth of which depends on the metal–particle distance. Below a critical well depth surface states exist, which may be occupied by a substrate electron to form a one-electron bond (Pollard, *Phys. Review*, 1939, **56**, 324); pairing with a second electron from the metal is considered improbable.

This model for covalent bonding in chemisorption does not explain the decreased paramagnetism or ferromagnetism observed during chemisorption on some metals, or the apparent dependence of catalytic properties on conditions at the metal Fermi surface. Adsorption by this mechanism may occur alongside the types already treated especially when the metal conduction band is narrow.

Summarising these conclusions on covalent bond formation, it appears that the process of chemisorption is most favoured and fastest at surfaces having the following characteristics: large electronic work function, large value of $g(-\phi)$, large positive $(\mathrm{d} \log_e g(\varepsilon)/\mathrm{d}\varepsilon)_{\varepsilon = -\phi}$ and presence at the surface of "atomic" orbitals in the Pauling sense.

(iv) *Real Bonds.*—Real bonds are formed by van der Waals, coulombic, and exchange forces acting together, all of which depend on the electronic structure of the solid, whether the adsorbate is molecule, radical, ion, atom, or activated complex. It is impossible to estimate the strength or rate of formation of a mixed bond by simple methods, and even in the case of the pure-bond types the models involving formal ionisation potentials, electron affinities, and work functions are not very satisfying. The problem deserves a thorough quantum-mechanical analysis which might eliminate a number of the hypotheses introduced above.

Apparently however positive-ion and covalent-bond formation have a similar dependence on the properties at the Fermi surface. Thus, when the rate-controlling step involves donation of an electron to the catalyst with exchange, or involves the surface concentration of a particle formed by such a process, then activity improves with increasing work function, level density, positive density gradient, or *d*-content of the bonding orbitals. There will be values of $|\phi - I'|$ and $|E' - \phi|$ at which the ionic contribution to the bond begins to predominate.

The reaction of saturated molecules or molecules of high ionisation potential is most likely to proceed, where possible, by mechanisms of the kind $C_2H_6 + H^+ \longrightarrow C_2H_5^+ + H_2$ or $C_2H_6 + H \longrightarrow C_2H_5 + H_2$ where the inert molecule is physically adsorbed (see Rideal, *Proc. Camb. Phil. Soc.*, 1939, **35**, 130) rather than by direct chemisorption with bond fission.

In reactions of low activation energy ($\sim$5 kcals. per mole) the variation of van der Waals free energy of adsorption with electronic structure, hitherto neglected, must be taken into account.

7. THE SPECIFIC ACTIVITY.

The foregoing analysis of simplified models suggested a special configuration for the active centre, while electronic-band theory and valency theory led to optimum values for the electron energy and level density at the Fermi surface. In particular when electron donation to the catalyst is involved at the rate-controlling step, " holes " in a *d*-band fulfil the electronic requirements and the free energy of activation at an active centre is a minimum. On the other hand if the rate-controlling step involves the positive ion as a reactant its concentration is a maximum under the same conditions. So far the electronic characteristics at an active centre have been taken equal to the average for the whole crystal, but, viewed from the atomic rather than the band standpoint, the holes in the *d*-band of a *d*-metal appear at lattice points as ions of short life. Mott and Jones (" Properties of Metals and Alloys," Oxford, 1940, pp. 192, 224) have inferred from magnetic data for pure nickel that either a pair of holes (Ni^{2+}) or none (Ni) are the preferred structures at a lattice point, but specific heat results fix the number at one (Ni^+; Mott, *Proc. Physical Soc.*, 1949, **62**, 416). In alloys having a constituent not normally possessing holes in its *d*-bands, *e.g.*, copper, zinc, or aluminium (" *s,p*-metals ") in nickel, the probabilities of a hole appearing at an *s,p*-atom or at a *d*-atom are not the same. Niessen (*Physica*, 1939, **7**, 1011) considered that the holes appear mainly in the *d* atoms except in copper–nickel and nickel–zinc alloys where the distribution is random. At present the problem remains unsolved.

In our ignorance a number of possibilities need examination. The model involves a binary alloy system of uniform crystal size when the surface is essentially bare and electron donation to the crystal is rate-controlling.

(a) *Holes Randomly Distributed and All Available.*—When the crystals are small the total number of holes may be available for reaction, since the tunnel effect should render interior holes accessible up to *ca.* 40 A. from the surface when the barrier is small.

The rate of reaction per unit is then

$$\propto \frac{nn_d^1}{A} \exp. [-b(I^* + \mu_e^s)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

where n is the number of atoms in the crystal, n_d^1 the number of holes per atom in the *d*-band at temperature $T°$ K. and *s,p*-metal atomic fraction x. μ_e^s is the thermodynamic potential per metal electron per unit volume in the alloy crystal and A its surface area.

(b) *Groups of* n *Holes, randomly distributed, Available only at the Surface.*—Although the tunnel effect enables an electron of suitable energy to reach all holes, the electrons considered here are not initially in the right state. The ionisation of the adsorbed species will be dependent on the powerful Coulomb field of the transient positive ion, and its effect upon the potential barrier will decline rapidly as the hole recedes from the surface due to the perfect shielding by the mobile electrons. The chance of finding a hole at a surface atom is proportional to the concentration of holes in the crystal and to the ratio of surface atoms (n_s) to the rest (n_r), *i.e.*, $\propto n_d^1 n_s/n_r$, or if the holes move in groups of y the chance of finding such a group in the surface becomes $\propto n_d^1 n_s/n_r y$ and the rate of reaction per unit area

$$\propto \frac{n_d^1 n_s}{n_r y A} \exp. [- b(I^* + \mu_e^s)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

(c) *As* (b) *but the Holes appear only at* d-*Atoms.*—The above equation must be multiplied by the atomic fraction of *d*-atoms giving a rate

$$\propto \frac{n_d^1 n_s}{n_r y A} (1 - x) \exp. [- b(I^* + \mu_e^s)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

In all the above examples the activity of an active complex has been put equal to the average for an active centre.

n_d^1 is itself a function of the alloy composition and for simplicity will be put $\simeq n_{0d}^1$ the corresponding value at 0° K., when for a binary alloy of a *d*-metal and an *s,p*-metal $n_{0d}^1 = (1 - x)n_{0d} - x(n_{0s} - {}_dn_{0s}) = (1 - x)n_{0d} - xn_s$. n_{0d} and ${}_dn_{0s}$ refer to the *d*-metal and are respectively the number of holes in the *d*-band and the number of *s,p*-electrons per atom. n_{0s} is the number of *s,p*-electrons per atom of *s,p*-metal and x is the atomic fraction of *s,p*-metal. At a critical composition (x^*), n_{0d}^1 becomes zero and the alloy activity can be considered in two parts corresponding to alloys having holes and those having none. If we use the (*b*) approximation and take first the *d*-metal-rich side of the critical composition, the total activity of unit area includes that of active centres with holes and active centres without holes. The activity of centres without holes is the same as that at the critical composition.

The rate of reaction at composition $x < x^*$ is then

$$\propto \frac{Z}{A}\left\{\frac{n_d^1 n_a}{n_r y} \exp. [- b(I^* + \mu_e^s)/kT] + \left(1 - \frac{n_d^1 n_a}{n_r y}\right) \exp. [- b(I^* + \mu_e^{s*})/kT]\right\} \quad . \quad (20)$$

where Z is the fraction of the surface occupied by active centres. In the range of composition where there are no holes ($x > x^*$) the rate

$$\propto \frac{Zna}{A} \exp. [- b(I^* + \mu_e^s)/kT] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

Since the activity term corresponding to holes in the *d*-band is such as to give a large activity, this must fall rapidly to a small value or zero (depending on the exponential containing x^*) at the critical composition.

At temperatures above 0° K. there is a transference of electrons from the *d*-band to the *s,p*-band in alloys such as copper–nickel (Wohlfarth, *Proc. Physical Soc.*, 1948, **60**, 360; *Proc. Roy. Soc.*, 1949, *A*, **195**, 434) so that $n_d^1 > n_{0d}^1$ and the sharp drop of n_{0d}^1 to zero at the composition x^* is replaced by a more gradual approach of n_d^1 to zero at a slightly different critical composition $x_1^* > x^*$. When the reaction is such that the holes in the *d*-band are very active and the filled band is effectively inactive, then the activity of the *s,p*-metal-rich alloys at $x > x^*$ will be very sensitive to small variations in n_d^1 brought about the thermal activation. Under these conditions

$$n_d^1 \propto \exp. (- \Delta\varepsilon/kT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (22)$$

where $\Delta\varepsilon$ is the difference in energy between the top of the *d*-band and the Fermi surface (Mott, *Phil. Mag.*, 1936, **22**, 287; Wohlfarth, *loc. cit.*).

Over alloys where the holes appear only at *d*-atoms, the initial decline in activity with increasing x is much more rapid than that given above, but reaches zero at the same value of x. Similar results obtain regardless of the valency of the *s,p*-metal in solid solution and the activity falls more quickly to zero at a smaller x^* with increasing Δn_e since $\partial n_{0d}^1/\partial x = -\Delta n_e$.

Relevant data on the alloys of *d*-metals amongst themselves are scanty and not always reconcilable with simple band theory. Here it will be assumed that the same general principles apply. In alloys containing no *d*-metal, *e.g.*, α-brass, the two metals appear to have a common *s,p*-band and the electronic structure of an active centre will be taken, in a first approximation, to be independent of nearest neighbour atom type.

The fact that vacant electron sites appear at specific atoms suggests the link between the electronic-structure effect in catalyses and the current purely geometric interpretations.

(d) *Retardation by Reactants and Products.*—The reaction rate trends given above may be said to be typical of the metal and not of the general class of catalyst–sorbate complexes. They hold for processes proceeding in a stationary state on a sparsely populated surface, or for the induction period of a reaction involving surface coverage by chemisorbed reactants or products. In a stationary state where some chemisorbed species covers an appreciable fraction of the surface, the rate-controlling step may proceed on the bare surface or it may involve the removal of the chemisorbed material itself; both situations are normally treated by the methods initiated by Langmuir. However, where the chemisorption of the retarding species involves increase of the electron : atom ratio of the crystal it affects the whole surface by reducing n_d^1 or by raising the electron energy in *s,p*-metals. In coherent catalyst crystallites of normal size the drop in activity from this cause should be small. On the other hand, when the rate-controlling step involves an attack on the retarding layer itself, the local concentration of electrons or holes at its periphery will tend to be larger or smaller respectively than in the crystal bulk, and the reaction rate may be slower than expected. That is to say the strongly chemisorbed molecules function in the same way as *s,p*-metal, and displace the rapid onset of activity in *d*-metal alloys to values of x lower than x^*, or in *s,p*-metal alloys produce a lowered activity corresponding to a higher electron : atom ration than actually present in the bare alloy.

All the foregoing major conclusions are reversed in an obvious manner when negative-ion formation is the rate-controlling step.

8. PURE METAL AND ALLOY CATALYSTS.

In this section the rules laid down will be applied to some real catalysts. A metallic catalyst is defined as one which *in situ* in its quasi-stationary state contains metal as a separate phase regardless of form or manner of support. When there is more than one metallic constituent the resulting alloys are assumed to be homogeneous, while in the presence of several metallic phases the total activity is taken to be a linear function of the percentage weight, specific activity, and specific area of each phase.

Metallic catalysts of industrial interest have almost-full or just-filled 3*d*-, 4*d*-, and 5*d*-bands, and our discussion shows that their activity must vary rapidly with composition in that range. The variation in physical properties is well known (Mott and Jones, *loc. cit.*). Less well known are the hydrogen solubility studies of Sieverts *et al.* (*Z. anorg. Chem.*, 1915, **92**, 329) in the silver–, gold–, and copper–palladium systems, where the solubility at low temperatures (10—100° c.) falls rapidly from the high value in palladium to almost zero at the equiatomic composition. There exist, also, less well defined properties which change with the filling of *d*-band holes and are probably associated phenomena, *e.g.*, the rate of oxidation (Pilling and Bedworth, *Ind. Eng. Chem.*, 1925, **17**, 372) and sulphuric acid attack (Irmann, *Abhandl. Inst. Metall., Aachen*, 1916, **1**, 39) on the copper–nickel alloys, the diffusion of nickel in copper (Johnson, *Metals Tech.*, Tech. Publ. No. 2007, 1946), etc. See also Uhlig (*Trans. Electrochem. Soc.*, 1944, **85**, 307) on corrosion.

(i) *Transitional Metals.*—Only the metals from chromium to zinc will be considered but the reasoning applies equally to the remaining members of the period and to the other long periods.

Calculation (Krutter, *Phys. Review*, 1935, **48**, 664; Manning, *ibid.*, 1943, **63**, 190) shows that the density of electron levels, $g(-\phi)$, increases steadily from chromium to iron. The low-temperature electronic specific-heat data of Keesom and Kurrelmeyer (*Physica*, 1940, **7**, 1003) indicate a flat in $g(-\phi)$ extending from α-iron to β-cobalt, a sharp rise between the solid solution 85 : 15 nickel–iron and pure nickel, and a rapid fall between the nickel–copper solid solutions containing 40% and 20% of nickel. Since the best recorded electron work functions may vary by as much as 0·5 ev. for a given metal only the trends in each period will be noted. There appears to be a relatively rapid increase of work function between the metals of group 5A and 8, followed by a constant or slowly increasing value up to nickel, palladium, or platinum in each period and a rapid fall to copper, zinc, etc. (Reimann, " Thermionic Emission," Chapman and Hall, London, 1934; Herring and Nichols, *Rev. Mod. Physics*, 1949, **21**, 187). Parallel changes occur in the inner potential, where it is known, and in the reciprocal of the metal interatomic distances. If the effects of increasing electron : atom ratio from copper to zinc are observed in the properties of the corresponding solid solutions (intermetallic compounds also in the copper–zinc alloys), the above trends show discontinuities at phase boundaries, and changes of slope where the gradient of $g(\epsilon)$ undergoes rapid change.

(a) *Rate controlled by positive-ion formation.* There will be a gradual increase in activity from chromium to cobalt, onset of high activity between the alloy 85 : 15 nickel–iron and pure nickel, and a sharp maximum either at pure nickel or in dilute solid solutions of iron and cobalt in nickel. Beyond nickel the activity drops almost linearly to a very low value at 40 : 60 nickel–copper (depending on the temperature and the reaction) and then decreases slowly still further to zinc.

A number of additional effects operate but it is difficult to estimate their magnitudes or to superpose them upon the general curve. Thus, according to Pauling and Ewing (*ibid.*, 1948, **20**, 112) the electron : atom ratios of both α- and β-manganese correspond to full or almost full Brillouin zones, and therefore their activities should be less than expected on simple interpolation between the activities of body central cubic chromium and α-iron [see section 8 (iii)]. In addition, the alloys and elements between pure nickel and 40 : 60 nickel–copper are ferromagnetic at those temperatures where the free metals are normally used as catalysts. This implies [section 8 (v)] the presence below the Curie temperature of an inhibiting effect, decreasing in the series cobalt, iron, and nickel, which must be included in the total assessment of activity.

(b) *Rate controlled by negative-ion formation.* The activity trend is the opposite of that discussed in (a) while the secondary variations can obviously be treated similarly.

(c) *Rate controlled by covalent-bond formation.* The table shows how the valency orbitals are occupied in the various elements according to Pauling (*Proc. Roy. Soc.*, 1949, *A*, **196**, 343).

Transitional-metal Orbitals (Pauling).

Orbital type.	Cr.	Mn.	Fe.	Co.	Ni.	Cu.	Zn.
Bonding (max. 6) filled	3·6	4·6	5·6	6	6	5·5	4·5
Atomic (max. 3) not full	0·22	1·22	2·2	1·7	0·6	Nil	Nil

The total number of singly occupied " atomic " orbitals reaches a maximum value at the alloy of approximate composition iron 77% and cobalt 23%, and falls to zero at an alloy containing nickel 40% and copper 60%. Therefore up to this latter composition *d*-orbitals are readily available at the surface to form strong bonds, but at higher electron : atom ratios only a fraction of the " bonding " orbitals, which are themselves decreasing in number, can be used. The activity changes must parallel these given under (a) and similar filled-zone and ferromagnetic effects will be apparent.

(ii) *Alloys of* d-*Metals with* s,p-*Metals and Metalloids.*—As an element with loosely held valency electrons is added in solid solution to a transitional element with holes in the *d*-band, the decrease in activity, when positive-ion or covalent-bond formation is rate-controlling, parallels the decline in the number of holes per atom in the *d*-band of the alloy. The rate of decrease depends upon Δn_s (cf. section 7), and is larger the higher the valency of the solute *s,p*-metal. Only in a number of simple cases can the band theory be used to predict in detail the characteristics at the Fermi surface of the alloys, and in more complex alloys recourse should be had to the physical (particularly magnetic) data themselves.

In the alloy composition range where $g(-\phi)$ begins to drop rapidly, the activation energy ($\propto I^* + \mu_e^m$) of the substrate reaction begins to increase because the rise of Fermi energy per added electron increases; the electronic contribution to the entropy of activation ($\propto dg(\varepsilon)/d\varepsilon$ at $\varepsilon = -\phi$) falls. This phenomenon occurs because of the extensive overlapping of energy levels in solids. Homogeneous reactions correspond largely to transitions between potential surfaces, in which the energy level density, and therefore also the entropy and the entropy factor, always increase with increasing energy and hence with activation energy.

The activity–composition relation holds whether the composition corresponds to an intermetallic compound or to a solid solution, and whether the range of solid solution is wide as in nickel–copper alloys, narrow as in tin–iron, very limited (iron–copper), or scarcely different from the chemisorption of the *s,p*-metal. Hydrogen, boron, carbon, nitrogen, phosphorus, and the metalloids function in the same way as the *s,p*-metals, but possible failure of the band theory when applied to their alloys and compounds suggests caution in fixing the effective valency at the normal chemical value. The effect of hydrogen in deactivating palladium (Beeck, U.S.P. 2,223,777) must be explained on this basis and the much disputed rôle of " bulk " carbide in the Fischer–Tropsch processes appears, at the least, to be that of a diluent.

When negative-ion formation is rate-controlling the activity changes are the converse of those given above.

(iii) *Hume-Rothery Alloys.*—Jones (*Proc. Roy. Soc.*, 1934, *A*, **144**, 225) has pointed out that the phase changes occur at special electron : atom ratios, when the Fermi surface can be reduced in energy because of the greater density of electron levels available at the Fermi surface in the new phase. Sharp changes in activity must be expected at the phase boundaries associated with the electronic readjustments and with the different geometry. The geometric contribution cannot be estimated but the electronic effects follow from the theory.

Consider the brasses, beginning at pure copper and adding zinc. At pure copper the first Brillouin zone is half full, but addition of zinc in solid solution increases the electron : atom ratio, the energy of the Fermi surface and the electron-level density [at first $g(\varepsilon) \propto \varepsilon^{\frac{1}{2}}$]. The gradient of level density, $dg(\varepsilon)/d\varepsilon$, is positive but its numerical value is small compared with that at the critical composition in the copper–nickel alloys. As the Fermi surface approaches and touches the zone boundary, $g(\varepsilon)$ increases more rapidly to a sharp peak and then falls off rapidly, so that the face-centred cubic structure has a decreasing value of $g(\varepsilon)$ and becomes unstable with respect to the body-centred cubic structure which possesses a large increasing value of $g(\varepsilon)$ at the same electron : atom ratio. The α-phase therefore rearranges to yield the β-phase, in which the level density at the Fermi surface increases, the gradient of level density changes from large negative to large positive, and the energy of the Fermi surface decreases (Fig. 4).

A similar description can be given of the changes at the boundaries of the β-phase with the γ-phase and of the γ-phase with the ε-phase.

(a) *Rate controlled by positive-ion formation.* The free energy of activation must increase up to the composition where the Fermi surface touches the zone boundary because the energy of activation increases with increase of Fermi energy and the electronic contribution to the entropy of activation is small but positive. [The gradient of $g(\varepsilon)$ must be very large to make an appreciable entropy contribution since it appears in the latter as $d \log_e g(\varepsilon)/d\varepsilon$.] Further increase of electron : atom ratio pushes the Fermi surface up to the peak in $g(\varepsilon)$, and this will be accompanied by a flattening of the rising activation free energy curve owing to a diminution in the rate of increase of the Fermi energy per added electron and to the increasing electronic entropy effect. As the Fermi surface passes under the peak of $g(\varepsilon)$ the situation is similar to that in the nickel–copper alloys, at the critical composition when the *d*-band is filling up, and a rapid increase in the free energy of activation results. However in the new phase the electronic characteristics are similar to (not identical with) those in the old phase at the composition where $g(\epsilon)$ is just rising to its peak. Thus at the boundary of the new phase the free energy of activation is considerably lower than that at the electron-rich edge of the old phase. This activity pattern repeats itself in each new phase as long as the structure is controlled by electron : atom ratio. In the intermediate regions of mixed phases a linear relation holds between the activities of the old and new boundaries (see Schwab, *loc. cit.*).

It is worth noting that in a given phase the activity variations between crystal faces of different Miller index will be most pronounced around the maximum in $g(\epsilon)$.

When negative-ion formation is rate-controlling the trends are the converse of those given above.

(b) *Rate controlled by covalent-bond formation.* Pauling's valencies lead one to suppose a gradual decrease of activity from copper to zinc through the brasses, but with oscillations about this average line corresponding to the phase changes. Band theory gives the same results as in (a).

(iv) *Order and Disorder in Alloys.*—Pauling and Ewing (*loc. cit.*) suggest that ordering in β-alloys may be affected by electron filling of Brillouin zones and this leads to conclusions on activity changes during ordering and disordering similar to those considered in subsection (iii). The state corresponding to a filled zone, or one filled to just past the peak in $g(\epsilon)$, should have the lowest activity in the absence of dominating geometric factors.

(v) *Magneto-catalytic Effect.*—Hedvall's observations (see *Chem. Reviews*, 1934, **15**, 139; *J. Physical Chem.*, 1942, **46**, 841; "Handbuch der Katalyse," edited by Schwab, Springer, Vienna, Vol. VI, p. 578) on activity changes as catalyst temperatures pass through the Curie point receive in part a very natural explanation according to this theory. Cardwell (*Phys. Review*, 1949, **67**, 125) has produced evidence of a small increase in the work function of pure nickel as its temperature increases through a region including the Curie point, and this together with the accompanying disorientation of the metal-electron spins indicates a change in catalytic activity. In a ferromagnetic metal at absolute zero all *d*-band holes are of one spin only and the energy required to uncouple an electron spin is $\sim k\theta_c$ where θ_c is the Curie temperature in °K. Addition of electrons to the metal (or formation of a covalent bond) near 0°K. with the lowest activation energy can occur only for electrons of one kind of spin, and in the absence of any orienting effect of the metal-electron–substrate-electron exchange energies this implies the reduction of the entropy factor by one half. Rising temperature uncouples an increasing number of spins so that the entropy factor increases and the rate constant contains a factor $(1 + \exp. - \theta_c/T)$. Above θ_c spins of both kinds can be paired in the *d*-band and the entropy contribution from this factor is a maximum; at the same time terms containing $k\theta_c$ drop out of the activation energy. Now in real polycrystalline metals the saturation magnetisation seldom falls to zero sharply at a specific temperature but "tails" to zero slowly over a finite temperature range (Gerlach, *Z. Elektrochem.*, 1939, **45**, 151). Over this range the entropy factor increases and the activation energy decreases in the manner described, whether positive-ion, covalent-bond, or negative-ion formation is rate-controlling; this is the magneto-catalytic effect.

If the effect noted by Cardwell (*loc. cit.*) is general, then this change in work function is an additional factor; it decreases the activation energy of reactions controlled by positive ions and increases the activation energy where negative ions are dominant.

Practically the effect can best be demonstrated on alloys of low Curie point where side reactions interfere least, but these are the catalysts where the effect will be a minimum. At higher temperatures side reactions (*e.g.*, carbide formation) confuse the issue, and the reaction between hydrogen and deuterium seems most suited to this study.

(vi) *Poisons.*—Three mechanisms of catalyst poisoning must be recognised although they are not entirely independent of each other.

(a) *Change of electron work function* (cf. Nyrop, *op. cit.*). Addition of strongly electropositive substances lowers the work function and poisons reactions proceeding *via* a positive ion at the slowest step, whereas strongly electronegative reagents poison the corresponding anion-controlled processes by raising the work function. Beyond a certain range of work function both types will poison reactions involving covalently bonded intermediates.

The rate of change of work function with surface concentration of poison is greatest when the concentration is small. Since the work function appears in the rate equation as an exponential, it can be seen that this model accounts quite well for those poisoning effects which have been used as evidence for the "non-uniform" surface. According to this view, even a uniformly active surface must exhibit a proportionally greater fall in activity on chemisorption of the first traces of poison than for the later portions.

(b) *Electron-level effects.* Multivalent elements with easily removable valency electrons, *e.g.*, mercury, lead, arsenic, antimony, tin, bismuth, etc., poison by forming surface alloys with metals having *d*-band holes, whereby the holes or orbitals are blocked with electrons. The poisoning effect is greater the larger the valency, other things being equal [cf. section (ii)]. In the Hume-Rothery-type alloys of metals without *d*-band holes, the effect of these added substances may be that of deactivation caused by a rapid rise of the Fermi energy per poisoning atom, or of activation when sufficient of the poison is added to precipitate a localised phase change with drop in free energy of activation [cf. section (iii)]. These remarks are true for reactions involving positive-ion or covalent-bond formation at the slowest step; the converse is true in an obvious way for anion formation.

A dipole must be expected at the surface under these conditions which will have an additional effect according to (a).

(c) *Steric effects.* Both (a) and (b) imply occupancy of active centres and surface coverage with all its geometric consequences.

(vii) *Special Metallic Catalysts.*—The earlier sections have described the properties of catalysts which are obviously metallic. There are other catalysts which behave as metals although the situation is more complex; two types and their possible mode of action will be described.

(a) *Reducible metal oxide plus "irreducible oxides."* Under reducing conditions, as in hydrogenation, the easily reducible metal oxide yields small metal crystals in a matrix of unreduced mixed oxides (*e.g.*, Cu in CuO.ZnO and in $CuCr_2O_4$), or the metal crystallites carry the unreduced oxides as inclusions and adhesions (*e.g.*, promoted-iron ammonia catalysts). At the same time, owing to the possibility of alloy formation between the reduced metal and the metal of the " irreducible " oxide, the free energy of that reaction is available to assist the reduction of the intransigent oxide. This holds even though the extent of alloy formation at equilibrium amounts to scarcely more than the chemisorption of the second metal. Thus with CuO.ZnO, small crystals of brass appear and the activity of copper is diminished; or in $CuCr_2O_4$ there may be a very small concentration of chromium dissolved in copper with production of holes in the copper *d*-band and an enhancement of activity. (Such catalysts are used at moderately high temperatures.)

" Alkalisation " of metal catalysts with alkali-metal compounds, such as the carbonates and hydroxides, is a common device in hydrogenations such as ammonia synthesis. Since the reactions take place at metal surfaces it seems that the function of the electro-positive metal must be to adjust the metal work function (see Brewer, *J. Amer. Chem. Soc.*, 1931, **53**, 74; 1932, **55**, 1888; *Phys. Review*, 1931, **38**, 401), the free alkali metal being supplied by a mechanism similar to that above.

(b) " *Irreducible* " *oxides.* In our approximation, only the oxides of beryllium, magnesium, boron, aluminium, and silicon are considered to be irreducible. Other oxides such as zinc oxide, are known to be defective in oxygen and to be excess semi-conductors even at considerable partial pressures of oxygen. At high pressures of hydrogen or carbon monoxide this reduction will be increased, although thermodynamic data show that no bulk metal phase can separate at ordinary temperatures ($<1000°$ c.). It seems possible that the metal atoms may form what amounts to a " dilute metal " in the oxide lattice, or they may separate into some essentially metallic surface phase, so that the catalysed reaction proceeds at a metal surface. When the oxygen-defective oxide is metallic its behaviour can be described by the principles of this section, and when it is a semi-conductor by those of following sections.

9. REACTION EXAMPLES.

Unfortunately there are no known reaction mechanisms in heterogeneous catalysis, and the application of the theory to given reactions can follow only the most general lines. As far as the scanty data go, hydrogen generally reduces the work function of group 8 metals (de Boer, " Electron Emission and Adsorption Phenomena," Cambridge, 1935, p. 149), which suggests that protons exist at the surface and that hydrogenation ought therefore to provide examples of mechanisms involving positive ions. In the same way surface reactions with oxygen or the hydroxyl ion should provide examples of anion-controlled reactions.

(a) *Hydrogen Addition at Multiple Bonds.*—Suppose that saturation of multiple bonds proceeds *via* one of the following steps which is rate-controlling (H_2, R, and RH_2 physically adsorbed; R is, *e.g.*, an olefin; the rest chemisorbed):

$$\begin{aligned} \tfrac{1}{2}H_2 &\longrightarrow H^+ + e \\ R &\longrightarrow R^+ + e \\ R + H^+ &\longrightarrow RH^+ \\ R^+ + H &\longrightarrow RH^+ \\ RH^+ + H_2 &\longrightarrow RH_2 + H^+, \text{ etc.} \end{aligned}$$

$$\begin{aligned} \tfrac{1}{2}H_2 &\longrightarrow H \\ R + H &\longrightarrow RH \\ RH + H_2 &\longrightarrow RH_2 + H \end{aligned}$$

The rate in the ionic mechanism is either that of the formation of a positive ion, or is proportional to the stationary concentration of a positive ion. The rates and concentrations depend upon the number and characteristics of holes in the *d*-band of a transitional metal as already described (section 7) and hydrogenation activity must fall to a low value as the holes are filled. Similar behaviour is to be expected if the intermediates are covalently bonded. The results of Rienäcker on the hydrogenation of ethylene (*Z. anorg. Chem.*, 1939, **242**, 302; 1943, **251**, 60) and cinnamic acid (*J. pr. Chem.*, 1941, **158**, 95), although not clear-cut, are in general accord with this picture.

(b) *Hydrogenolysis of Bonds.*—Bremner (*Research*, 1948, **1**, 281) has attributed the large effects in the hydrogenolysis of esters to a "protonolysis," and similar steps can be postulated for some alcohols, *e.g.*, $ROH + H^+ \longrightarrow R^+ + H_2O$ (rate-controlling), followed by $R^+ + H_2 \longrightarrow RH + H^+$. The reaction rate then depends on the surface concentration of protons, and the process may be slowed down or stopped by "alkalisation" [section 8 (vii)] which reduces the stationary work function of the metal surface. Components of acidic function such as alumina and silica may act by controlling the alkali-metal concentration through equilibria equivalent to $Na_2O + Al_2O_3 \longrightarrow Na_2Al_2O_4$, etc., and it should be possible to adjust the work function of the composite surface over a wide range (see Brewer, *loc. cit.*).

Conversely hydrogenolysis should be promoted by small concentrations of electronegative reactants such as hydrogen sulphide, provided that the surface coverage is so small that complete blocking of active centres does not occur.

(c) *Anions in Copper–Nickel Alloy Oxidation.*—A class of reaction where negative ions certainly participate is the oxidation of metals, and it is interesting to note that Pilling and Bedworth (*loc. cit.*) found large changes in rate between 20% and 70% of nickel in copper–nickel alloy oxidation at high temperatures (850—1000° c.). The oxidation rate is fairly constant up to between 30 and 40% of nickel at 850° and 900°, but then begins to fall off rapidly and approaches a much lower limiting value at 60—80% of nickel, depending on the temperature.

It may be significant that this decrease in reaction velocity begins close to the composition where the *d*-band of the alloys starts to empty and suggests that the rate-controlling step in this region involves the passage of electrons from the metal Fermi surface to oxygen to form the corresponding anions.

(d) *Electron Transfer in Hydrogen Peroxide Decomposition.*—Weiss (*Trans. Faraday Soc.*, 1935, **31**, 1547) in a continuation of earlier studies on the catalysed decomposition of hydrogen peroxide (Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 332) suggests that with metal catalysts the rate-controlling step is H_2O_2 + metal electron $\longrightarrow OH^- + OH$. The theory predicts therefore that over copper–nickel alloys the decomposition rate will be fastest on copper and copper-rich alloys, falling to a lower value as the *d*-band begins to empty in the neighbourhood of 40% of nickel. This applies at hydrogen-ion concentrations where the alloys are not attacked, and on bare metal surfaces where the oxide film is not thick enough to prevent the electron transfer.

10. SEMI-CONDUCTORS.

Many solid catalysts employed in reactions involving reducing and oxidising gases have some metallic characteristics or are semi-conductors *in situ* in the stationary state. This is qualitatively apparent in the radical colour changes undergone by "irreducible" oxides and sulphides on activation or in use, to yield black, lustrous, or highly coloured contact masses. It is significant also that these semi-conductors are much less active, for instance in hydrogenation, than metals at the same low temperatures and are not nearly so sensitive to poisoning by sulphur and its compounds.

Unfortunately these oxide and sulphide catalysts are amorphous in the most active forms and their structure can only be guessed, whereas metal catalysts are often recognisably crystalline by ordinary techniques. The bonding of the chemisorbed species at the semi-conductor surface must nevertheless follow the same principles as with metals, but the electronic characteristics are considerably different and the already complex substrate reactions are augmented by others in the solid. A convenient classification of catalysts follows that devised for the discussion of the electrical properties, namely as intrinsic, normal, and abnormal semi-conductors (see Mott and Gurney, "Electronic Processes in Ionic Crystals," Oxford, 1940; Seitz, "Modern Theory of Solids," McGraw Hill, New York and London, 1940). The last two kinds arise most simply under hydrogenating and oxidising conditions respectively, while many oxides and sulphides can exist in both forms depending upon the partial pressure of the electronegative element in the gas phase. In the following discussion the oxide and sulphide stoicheiometric lattices are

assumed to be purely ionic; covalent and van der Waals contributions to the inter-ionic forces are neglected without, it is believed, detracting from the validity of the results which can in any case be only of a general character. If greater detail is required, then the basic ideas must be applied to special systems along the lines followed by Mott and Littleton (*Trans. Faraday. Soc.*, 1938, 34, 485), Seitz (*Rev. Mod. Physics*, 1946, 18, 384), and Wright (*Proc. Physical Soc.*, 1948, 60, 13) in studies on the solid alkali and silver halides and group 2 oxides.

(i) *Positive-ion Formation.*—Production of positive ions during chemisorption at the surface occurs, as in metals, by transfer of an electron from the filled substrate level of highest energy to the empty crystal level of lowest energy. Appropriate thermodynamic potentials for the electrons in a semi-conductor are used (see Fowler, " Statistical Mechanics," Cambridge, 1936) and conclusions are formed analogous to those found for metals. Only an outline of principles and inferences is given in the succeeding sections.

(a) *Intrinsic semi-conductors* (Fig. 5). One may suppose that few catalysts function by a purely intrinsic mechanism, but it is useful to discuss this type first because it forms a basis, small modifications of which lead to the other catalyst types.

FIG. 5.

Electron levels in an insulator or intrinsic semi-conductor (idealized).

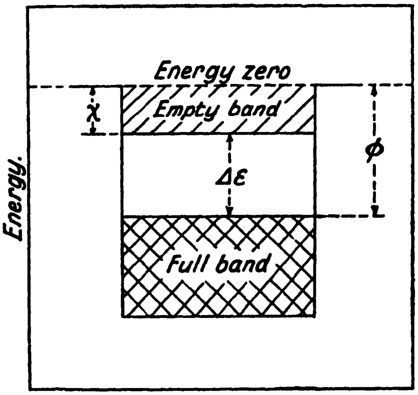
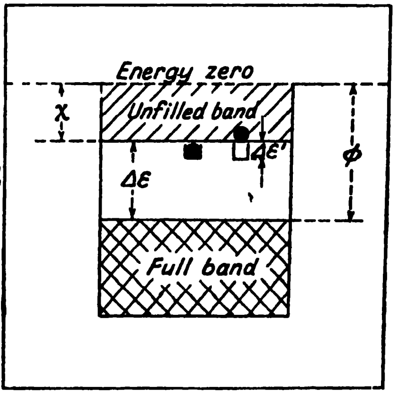


FIG. 6.

Electron levels in a normal semi-conductor (idealized).



In these solids the top (energy $= -\phi$) of the filled electron band is separated from the bottom (energy $= -\chi$) of the empty band by a forbidden energy region $\Delta\varepsilon \sim kT$, and the formation of holes in the filled band by thermal activation of electrons to empty levels is not dependent on non-stoicheiometry or impurities. At any absolute temperature T, the concentration of holes at the top of the filled band and of electrons in the empty band is $\propto \exp. [-\Delta\varepsilon/2kT]$. The holes, which may be in the filled band of the cation or anion whichever lies higher, are the acceptor levels of lowest energy, while the electrons promoted to the empty band lie in the donor levels of highest energy; both holes and electrons are mobile and can appear at the surface. For a given substrate the energy of activation for positive-ion formation is readily shown to be $\propto (I^* - \phi + \Delta\varepsilon/2)$ where I^*, equal to $I + \Delta U^*$, is the ionisation potential of the activated complex and the activation energy decreases as ϕ increases and $\Delta\varepsilon$ decreases. When the catalyst lattice is ionic, $\phi = A_a e^2/a + E_a - \omega_h$, $-\chi = A_c e^2/a - I_c - \omega_e$ (see Mott and Gurney, *op. cit.*) where A_a and A_c are the Madelung potentials at anion and cation sites respectively, ω_h the polarisation energy around the electron hole, ω_e that around the excess electron, E_a is the least energy required to remove an electron from the anion *in vacuo*, I_c is the energy gained on adding an electron to the cation *in vacuo*, e is the electronic charge, and a the unit cell parameter. Therefore, $\phi - \chi = \Delta\varepsilon = (A_a + A_c)e^2/a + E_a - I_c - \omega_h - \omega_e$, and in binary compounds, where anion and cation exert the same electrovalence, $\phi - \frac{1}{2}\Delta\varepsilon \simeq (E_a + I_a)/2$ if polarisation effects are neglected. Thus on the assumption that the anion-filled band lies higher than that of the cation, the activation energy decreases as E_a and I_c increase. The full expression for $\Delta\varepsilon$ shows how it depends on the Madelung potentials and reveals that $\Delta\varepsilon$ is smaller in the surface plane owing to the reduced values of A_a and A_c in that region.

Among the catalysts of bivalent metals the effect should be apparent in cupric, mercuric, nickel, and zinc oxides where the atoms have the highest second ionisation potentials in the periodic table, and particularly in the corresponding sulphides because of the smaller negative value of the S^- electron affinity compared to that of O^-. Unfortunately these metals are multivalent or reducible and the intrinsic phenomena are masked by others, described below, arising from non-stoicheiometry; the ionic oxides having a very small potential variability of composition are insulators because of the large values of $\Delta\varepsilon$. The discussion indicates that the intrinsic semi-conductors of most use will be almost metallic in properties, and these are found amongst the metalloids and intermetallic compounds having ionic character. Their catalytic properties follow most readily by extending the arguments used for the Hume-Rothery alloys to compounds where the full and empty bands are separated by a small energy gap in all lattice directions. In this way the electronic entropy factor can be reintroduced and shown up in its dependence on $dg(\varepsilon)/d\varepsilon$, for semi-conductors and insulators, as for metals.

The value of the activation energy depends also upon ΔU^* and therefore on ΔU^+ which has its largest value when the substrate positive ion is adsorbed over a vacant cation point in the surface lattice. The significance of this factor will be remarked in the next section concerning a more important type of semi-conductor.

(b) *Normal semi-conductors* (Fig. 6). Here the energy bands are similar to those in intrinsic semi-conductors, but the localised occupied electron level occurs close to the bottom of the empty band and separated from it by an energy $\Delta\varepsilon'$. The number of empty localised levels in a given volume at temperature T is proportional to both the volume and energy densities of levels and to exp. $[-\Delta\varepsilon'/2kT]$; these are the acceptor levels of lowest energy. Although the promoted electrons can migrate to the surface, the emptied levels are unable to do so, and only centres in or near to the surface are of interest in catalysis.

For a given adsorbate yielding a positive ion, the activation energy for chemisorption is now $\propto (I^* - \phi + \Delta\varepsilon - \Delta\varepsilon'/2)$ and this is minimised by the conditions noted under (a) but with additional parameters affecting $\Delta\varepsilon'$. The localised levels may be due to impurities or to a small excess of the lattice metal. Amongst oxide and sulphide non-stoicheiometric semi-conductors of the type found under reducing conditions, $\Delta\varepsilon'$ is very small (see particularly Fritsch, *Ann. Physik*, 1935, **22**, 375, the extensive review by Meyer, *Z. Elektrochem.*, 1944, **50**, 274, and Mott and Gurney, *op. cit.*) so that the probability of substrate ionisation by electron donation to these vacated localised levels is even less than that at the surface of an intrinsic semi-conductor having the same values of ϕ and $\Delta\varepsilon$.

The loss of electronegative constituent to give the reduced lattice is accompanied by displacement of metal atoms into interstitial positions (Frenkel, *Z. Physik*, 1926, **35**, 652) or by formation of anion defects (de Boer, *Proc. Physical Soc.*, 1937, **49**, extra part, 59; cf. Schriel, *Z. anorg. Chem.*, 1937, **231**, 313); neither model possesses cation vacancies to adsorb positive ions. Thus electron level energy, cation adsorption energy, and active centre requirements for positive ion formation apparently cannot be met in simple, normal semi-conductors of the zinc oxide type at the conductivity centres. However if substrate ions are formed by donation of electrons to the unreduced lattice cations, or to anion defects (producing F-centres), the activation energies may become reasonable. Consider a stoicheiometric zinc oxide crystallite containing its equilibrium quantity of intrinsic Schottky defects (Schottky, *Z. physikal. Chem.*, 1935, *B*, **29**, 335); cation and anion vacancies occur in equal but small concentration. Hydrogen might react with the lattice in several ways: it may yield hydroxyl ions, Zn^+, and zinc metal, or form Zn^+ or F centres (Mott and Gurney, *op. cit.*) with the protons adsorbed at cation defects, etc.

The proton is of course most strongly adsorbed as OH^- or when situated at a cation vacancy, but may be adsorbed with a sufficient energy at other general positions bridging anions by virtue of the powerful polarisation it produces. Substrates yielding larger positive ions require cation vacancies and, as already indicated, these are present only in small concentration in the stoicheiometric crystal and are still fewer in the reduced, semi-conducting state.

Positive-ion-forming processes can be encouraged, other things being equal, only by maintaining or increasing the concentration of cation vacancies by cutting down the extent of lattice reduction in the equilibrium state, or by adding or forming an irreducible ionic compound in which the cation defect is large and permanent. These modifications are affected simultaneously by "supporting" the semi-conducting oxide upon, or combining it as a solid solution or compound with, an irreducible oxide possessing the incomplete spinel lattice, *e.g.*, γ-Al_2O_3 (Verwey, *J. Chem. Physics*, 1935, **3**, 592) and possibly amorphous Cr_2O_3 (cf. Visser, *Chem. Weekblad*, 1946, **42**, 127); other suitable cation-defective reagents include the amorphous glass-like oxides such as silica and the mixed alumina–silica oxides where the network-modifying positions are empty (see section 11 on insulators).

Small amounts of sulphur cannot have a drastic effect on these lattices, and such lattices are not poisoned as are metal lattices by traces of this element. On the other hand alkali-metal ions and the like, which block cation defects, will function as poisons in reactions controlled by the rate of formation of a positive ion or by the surface concentration of a positive ion.

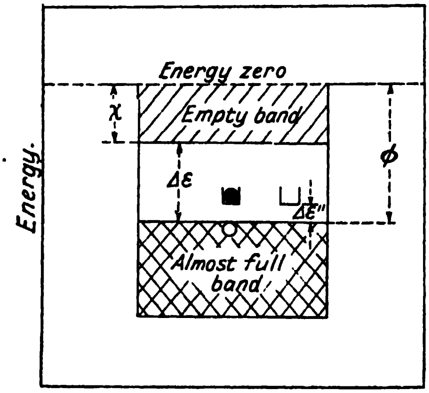
(c) *Abnormal semi-conductors* (Fig. 7). Abnormal or oxidation semi-conductors have in the forbidden region an empty localised electron level close to the top of the full band and separated from it by a small energy increment $\Delta\epsilon''$. The number of holes per unit volume in the top of the full band at any temperature T is proportional to the volume and energy level densities and to exp. $[-\Delta\epsilon''/2kT]$, and these are the acceptor levels of lowest energy. Here the empty localised levels, existing through non-stoicheiometry or impurities, are immobile and only those at or close to the surface can function directly as acceptor levels. The holes in the full band are mobile and can migrate to the surface.

The activation energy for positive-ion formation is now $\propto (I^* - \phi + \Delta\epsilon''/2)$ and is a minimum for a given substrate when ϕ is a maximum and $\Delta\epsilon''$ is a minimum. For oxide and sulphide catalysts where conductivity ensues from a big excess of the electronegative constituent, $\Delta\epsilon''$ is usually small compared to $\Delta\epsilon$ (*e.g.*, Cu_2O; Juse and Kurtschatow, *Physikal. Z. Sovietunion*, 1933, **2**, 453; Mott and Gurney, *loc. cit.*) so that the activation energy is approximately $(I^* - \phi)$ and, other things being equal, this class of semi-conductor is most likely to induce positive-ion formation. The incorporation of excess of oxide or sulphide into the lattice requires an increase in the positive charge at a number of cations and the omission of cations from a number of other lattice points according to $M^+(s) + \frac{1}{2}X_2(g) \longrightarrow M^{2+}(s) + X^-(s) + h^+$. The cation vacancies ($h^+$) in the surface are the active centres at which ΔU^+ will be greatest and I^* a minimum.

While such non-stoicheiometric semi-conductors may be formed from appropriately chosen catalysts in oxidation reactions, they are not likely to be present in the reducing atmospheres of reactions involving hydrogen and hydrocarbons. Under the latter conditions one might choose an irreducible basis oxide and support upon it a second multivalent metal oxide so that the " valence induction " effect (Selwood *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 883, 2145, 2271; Report of the Pittsburgh International Conference on Surface Reactions, 1948, p. 49) stabilises to some degree the oxidised state of the supported oxide. At least the basis oxide should possess stable cation defects, and the supported oxide also if possible.

FIG. 7.

Electron levels in an abnormal semi-conductor (idealized).



(ii) *Negative-ion Formation.*—Negative-ion formation is most easy and fastest for a given substrate when the electrons in the catalyst are loosely held. On intrinsic semi-conductors this means when both ϕ and $\Delta\epsilon$ are small. Subsection (i,b) (p. 260) indicates that normal semi-conductors should form negative ions readily since the electrons in the localised levels are situated relatively high in energy and are raised to the conductivity band, where they are comparatively free, with only a small energy input. Moreover there are anion vacancies to act as active centres and to increase the value of the anion adsorption energy.

Lattices which become abnormally semi-conducting in an oxidising atmosphere will affect substrate negative-ion formation by a process converse to that for positive-ion production at normal semi-conductor surfaces [see (i,b)]. Just as the latter reaction is more favoured in equilibrium and accelerated by the presence of structures with extensive stable cation defects, so should the former be assisted by stable extensively-anion-defective compounds. Not many representatives of this last kind are known at present but mention should be made of the compounds of bismuth oxide, Bi_2O_3, with lead, cadmium, and alkaline-earth oxides (Sillén and Aurivillois, *Z. Krist.*, 1939, **101**, 483; Sillén and Sillén, *Z. physikal. Chem.*, 1941, *B*, **49**, 27; Aurivillois, *Arkiv Kemi, Min., Geol.*, 1943, **16**, *A*, No. 17).

(iii) *Covalent-bond Formation.*—Covalent bonding in chemisorption must follow rules fundamentally similar to those given for metals, but there exists in the more complex oxides and sulphides considerable variation on that comparatively simple theme. Thus in addition to the simple bonding, arising for instance from use of the empty orbitals at the top of an almost full anion band in an abnormal semi-conductor to form single electron bonds, there are chemisorptions of the type $CO_2(g) + O^{2-}(s) \longrightarrow CO_3^{2-}(s)$ studied by Garner (*J.*, 1947, 1239).

11. INSULATORS.

As already suggested in section 10 (i,a), electron-transfer processes are not expected at ordinary catalyst temperatures on insulators, except to a minor extent at mechanical and intrinsic defects. The ionic insulator catalysts include chiefly the solid oxides and halides of the lower elements of groups 3, 4, and 5 of the periodic table. As a class they bring about reactions such as dehydration, isomerisation, polymerisation, cracking, etc., a most striking feature of which is the analogy with the corresponding homogeneous processes catalysed by strong acids, aluminium halides, and so on, increasingly described by carbonium- and oxonium-ion mechanisms in current literature (Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3274; Ciapetta, *Ind. Eng. Chem.*, 1945, **37**, 1210; Schmerling, *J. Amer. Chem. Soc.*, 1944, **66**, 1422; 1945, **67**, 1438, 1778; 1946, **68**, 275; Oblad and Gorin, *Ind. Eng. Chem.*, 1946, **38**, 822; Gorin, Kuhn, and Miles, *ibid.*, p. 795; Oblad, Messenger, and Brown, *ibid.*, 1947, **39**, 1462; Hansford, *ibid.*, p. 849; Bremner, *Research*, 1948, **1**, 281). It is significant in this respect that the oxide catalysts are of low activity in hydrocarbon reactions if their small water content is further reduced (see Hansford, *loc. cit.*) and if the water is looked upon as a source of protons. When pure these oxides are very poor hydrogenation, dehydrogenation, and oxidation catalysts. They are invariably colourless, as expected, and are notable glass-formers and ion exchangers; alkali-metal ions are strong poisons (Clark, Graham, and Winter, *J. Amer. Chem. Soc.*, 1925, **47**, 2748; U.S.P. 2,333,903; cf. Bremner, *loc. cit.*). Unfortunately the majority of the catalysts are amorphous with unknown lattice structures; except for active γ-alumina which has the defective spinel lattice (Verwey, *J. Chem. Physics*, 1935, **3**, 592) and related catalysts, they will be assumed to have glass-like skeletons (Zachariasen, *J. Amer. Chem. Soc.*, 1932, **54**, 3841; Hägg, *J. Chem. Physics*, 1935, **3**, 42; Weyl, *J Soc. Glass Tech.*, 1943, **27**, 133) from which the normal network-modifying ions are absent, the resulting cation vacancies and some anion bridge positions being occupied by protons.

γ-Alumina appears to occupy a unique position in the study of insulator catalysts since a number of workers confirm that activity is attributable to γ-Al_2O_3 which changes to α-Al_2O_3 at elevated temperatures (cf. Visser, *Chem. Weekblad*, 1946, **42**, 127; B.P. 571,352, 572,110; Feachem and Swallow, *J.*, 1948, 267; Fricke, Niermann, and Feichtner, *Ber.*, 1937, **70**, 2318) and they have associated activity with cation vacancies in general terms. In the following theory the properties of γ-alumina are taken to provide the clue to insulator activity which, it is asserted, arises principally from cation vacancies and possibly to a lesser extent from anion vacancies.

If carbonium- and oxonium-ion mechanisms are accepted as roughly correct for the characteristic reactions, they should be fastest at surfaces capable of forming and retaining carbonium ions through proton addition or exchange. Active surfaces must be those with cation defects, and the defects are the active centres since they possess the closest approximation to the geometry suggested in earlier sections. The free energy of chemisorption of a positive ion at a cation defect will increase as the electrostatic potential at a cation lattice point increases. In defective lattices, such as the defective spinel or a glass, it is usually assumed that the cations are distributed statistically over all the interstices of suitable radius. Although this is not likely to be an exact description at all temperatures, it does indicate that cation defects in the surface may have only a moderate life at a given lattice point. Now let the lattice contain a little water accommodated as hydroxyl groups, where the hydrogen may form hydrogen bonds with adjacent anions, then periodically, as a nearest neighbour cation site becomes empty, a proton will occupy the vacancy. At the lattice surface a cation defect has lost at least one of its anion nearest neighbours, and the deficit is made up by a substrate molecule held by polarisation forces somewhat larger than simple van der Waals forces. A proton, adjacent to the surface cation defect, now distributes itself amongst the cation point, nearest neighbour anions, and the substrate molecule according to their respective proton affinities in the solid and adsorbed phases. Thus a chemisorbed carbonium ion of definite life is formed directly from a sorbed olefinic reactant and will isomerise to the carbonium ion of greatest resonance energy (isomerisation), add to an adjacent physically adsorbed molecule (polymerisation), or to benzene and saturated hydrocarbons (alkylation), and so on. Similarly the oxonium ions derived from alcohols form carbonium ions with loss of water, and olefins are produced as the proton returns to a defect from the carbonium ion.

At low temperatures, when the mobility of the lattice cations is small, the life of surface cation defects is long, and the life of the corresponding chemisorbed complex will be controlled almost solely by the proton affinities already mentioned. On rise of temperature, cation vacancies have a much shorter existence, and the history of the chemisorbed complex will be affected by the intrusion of metal cations and the increased chance of the close approach of another defect. As a lattice cation moves into a vacancy the proton switches *via* the surrounding anions (forming OH^-) to the lattice vacancy in its new position, the net result being that the proton tends to follow the vacancy. In the presence of sufficient water, therefore, every defect possesses at least one associated proton : hydrous γ-alumina must contain at least 2·2% of its weight as water for this to be true. Occupation by a metal cation of a surface vacancy, chemisorbing the proton–substrate complex, results in the proton following the vacancy away from, or along, the surface by the mechanism described. It may happen however that the proton remains with the substrate as a positive ion and returns to a surface vacancy at some point other than that of its origin. The effect in the case of hydrocarbon residue is that of a charge migration along the chain. High temperatures increase cation mobilities exponentially and therefore shorten the life of cation defects; at the same time the decreased equilibrium water concentration reduces the fraction of vacancies containing associated protons. Under these conditions direct scission of a substrate into a positive ion chemisorbed at a vacancy and a negative ion held by polarisation forces is increasingly probable (cf. Eyring, Hulbert, and Harman, *Ind. Eng. Chem.*, 1943, **35**, 511).

The activity of all solid insulator catalysts whether oxides or halides can be interpreted on this basis although there is no evidence as yet for the presence of cation defects in the well-known pure-halide catalysts. Activity and specificity with a given substrate depend on the surface density of cation vacancies, the electrostatic potentials at the vacancies, and their nearest neighbour anions, and the fraction of vacancies containing protons. For different substrates the effective variables are the proton affinities and the radii of molecules and fragments. Even though these parameters are not independent, it is convenient for classification to consider them separately.

(i) *Cation-vacancy Density.*—The density of cation defects should be adjustable along the lines used by Koch and Wagner (*Z. physikal. Chem.*, 1937, **38**, *B*, 295) in their studies on the silver halides. If we confine our remarks to the oxides (although they are of general applicability), this requires the solid solution of a metal oxide of high valency in the lattice of one of lower valency. The extent of such solid solution is usually small, but in the amorphous oxides it may be appreciably larger owing to the metastability implied in their glassy structures, because of the very extended surfaces where geometric restrictions will be less than in the bulk, and because of the cross-linking by hydrogen bonds. This process of cation replacement requires that a number of cations of lower valency should be omitted from the lattice; the resulting vacancies are the active centres.

Alternatively, the solute may contain an anion of lower charge than the oxygen ion, and the fluoride ion is almost ideal in that it has almost the same radius as O^{2-} and OH^-. Addition of, say, aluminium fluoride in solid solution to aluminium oxide might result in the dropping of some Al^{3+} from the lattice with creation of active vacancies. Even in favourable circumstances it is unlikely that solid solution can be pursued indefinitely : it will eventually result in the lattice breaking down into two or more solid solutions or compounds (cf. Anderson, *Proc. Roy. Soc.*, 1946, *A*, **185**, 69) some or all of which may retain cation defects. The vast number of possibilities of cation defect in compounds is too large to be covered in a discussion of this kind and recourse should be had to reviews such as those of Laves (*Z. Krist.*, 1930, **73**, 202), Strock (*Z. Krist.*, 1936, **93**, 285), Anderson (*Ann. Reports*, 1946, **43**, 104), and Wells (*Quart. Reviews*, 1948, **2**, 185).

Catalyst poisons include all those agents which occupy surface cation vacancies irreversibly, *e.g.*, alkali-metal ions introduced during preparation of γ-Al_2O_3, alumina–silica gels, etc. Generally all ions which take up " network-modifying " positions in glasses should be poisons, and those taking up " network-forming " positions should be mild promoters or deactivators depending on the reaction. Many ions can take up both sorts of position (see Weyl, *loc. cit.*), but with the present lack of understanding of catalyst preparation processes it is impossible to foretell the distribution of a particular ion in a freshly prepared catalyst (cf. Plank and Drake, *J. Colloid Sci.*, 1947, **2**, 399, 413). More empirically, it can be seen that all oxides the radius ratio (cation : anion) of which is less than 0·414 are glass-formers (Kuan-Han Sun and Silverman, *J. Amer. Ceram. Soc.*, 1942, **25**, 97) and should possess maximum activity; pure oxides outside the group BeO, B_2O_3, SiO_2, P_2O_5, and perhaps GeO_2 will possess much smaller activity on this basis. Network-formers include such oxides as Al_2O_3, TiO_2, ZrO_2, ThO_2 SnO_2, ZnO, and maybe As_2O_5, which presumably enter the network of polyhedra in the catalyst gels as in glasses; the pure oxides (except Al_2O_3) will be less active than the glass-forming group because the tendency to random linking of polyhedra, and therefore the concentrations of cation defects is less. Other reasons will be given in the next section. Similar conclusions hold for the fluorides, or mixed lattices in which some oxygen ions have been replaced by fluorine ions; beryllium fluoride as a glass-former also yields somewhat unstable gels and is a typical borderline case. Fluorine ions however cause weakening of the polyhedra networks (Weyl, *loc. cit.*) so that fluorine-containing catalysts will be unstable compared to those containing only oxygen ions and will tend to crystallise and lose hydrofluoric acid with loss of both protons and cation vacancies at higher temperatures. Temperature stability can be improved by addition of sufficient alkali-metal or alkaline-earth oxides to stabilise the network or the defective spinel (*e.g.*, " β-alumina," Beevers *et al.*, *Z. Krist.*, 1936, **95**, 472; 1937, **97**, 59; B.P. 571,352, 572,110); such incorporations must be made in the catalyst bulk and not merely at the surface, with inevitable reduction of the number of cation vacancies. Moreover at higher temperatures ThO_2, SnO_2, ZnO, and to a lesser extent TiO_2 and ZrO_2, are reducible either completely (SnO_2), or in the semi-conductor sense (TiO_2, ZrO_2, ThO_2) and cause unwanted side-reactions which may be hindered by increasing the partial pressure of water vapour in the stationary state.

(ii) *Electrostatic Potential at a Vacancy.*—The proton affinity of an active centre is fixed, in the absence of covalent binding, by the proton affinity of the anion *in vacuo* and the electrostatic potential at the cation and anion sites. The calculations of Verwey and Heilmann (*J. Chem. Physics*, 1947, **15**, 174; 1948, **16**, 1091) show that the Madelung potential at the tetrahedral interstices is almost twice as great as that at the octahedral interstices in some spinel structures. In defective spinel lattices containing traces of water this situation can hardly be affected and the two sorts of cation vacancy will have different proton affinities with protons preferring the empty tetrahedral interstices. Thermal motion, gross structural defects, and the like will spread these proton levels out into narrow bands without displacing them appreciably. In the less crystalline glasses and " gels " a given cation defect will have a definite co-ordination number, but different defects may have co-ordination numbers varying slightly about the average, so that in the amorphous catalyst the proton affinity of the surface will vary over a wider range than at a crystal surface. Following Verwey and Heilmann (*loc. cit.*), it appears that tervalent and quadrivalent ions, in accordance with electrostatic rules, prefer octahedral interstices, while some tervalent ions such as Fe^{3+}, In^{3+}, and Ga^{3+}, along with a few bivalent ions (Zn^{2+}, Cd^{2+}), prefer tetrahedral interstices. This should provide in the defective γ-spinel structure a method for controlling the availability of the two types of vacancy; for instance, in a process deemed to require a vacancy of low proton affinity, as perhaps in a hydrocarbon reaction, the tetrahedral interstices might be blocked. Extension to amorphous catalysts is essentially simple but lack of data enforces again the use of approximations based on the properties of the relevant ions in the glasses, ion exchangers, etc.

Replacement of one or more vacancy nearest neighbour cations by one of higher charge reduces the negative potential at the vacancy and also its proton affinity. The rules affecting such substitutions have been noted above, and the possibilities depend on the co-ordination number of the site concerned. In the same way replacement of a nearest neighbour anion by one of lower charge also reduces the vacancy proton affinity. The same effects will occur regardless of the structure containing the vacancies and permit, ideally, variation of the lattice proton affinity over a wide range when polarisation is taken into account; in fact geometric restrictions arise, as mentioned in (i) (p. 263). Hansford (*loc. cit.*) and more recently Weiss (*J.*, 1948, 2164) have used Pauling's concept of electrostatic bond strength (see " The Nature of the Chemical Bond," Cornell, 1942, p. 386) to give a qualitative account of changes in the lattice " acidity," but the picture provides no model for the active centre and could be made quantitative only along lines similar to those suggested above.

Generally, increasing cation radius reduces the proton affinity at a vacancy in the pure lattice and may be another factor in the decline of catalytic activity of this kind as groups 2, 3, 4, and 5 of the periodic table are ascended.

(iii) *Proton Density.*—On the foregoing grounds ionic reaction mechanisms require protons. At low temperatures retained structural water is sufficient, but at high temperatures a partial pressure of water in the gaseous reactants may be required. Conversely, in hydrations in the liquid-phase or at high pressure, the catalyst may lose activity owing to complete hydration of the lattice with disappearance of all defects and change of lattice. The proton concentration can be raised by ion exchange with acids, by incorporating strong acids into the lattice, or by adding gaseous hydrogen to the reactants and a metal or semi-conductor to the solid phase. The last method would require a standard of control beyond that available at present.

Poisons include all substances of high proton affinity which compete with the substrate for protons and yield strongly chemisorbed positive ions (Bremner, *loc. cit.*). In the same way, molecules possessing a large affinity for carbonium ions (*e.g.*, benzene) are catalyst poisons.

Analogous reasoning leads to the conclusion that, under suitable conditions, anion-defective lattices, or lattices able to sustain an anion defect, should catalyse processes involving anion intermediates. The chief difficulty is that the known anion-defective structures (see Sillen *et al.*, *loc. cit.*; Zintl *et al.*, *Z. anorg. Chem.*, 1939, **240**, 145, 150; 1939, **242**, 79; Croatto *et al.*, *Gazzetta*, 1943, **73**, 257; 1948, **78**, 83, 95) are crystalline and not easily prepared with a large specific area.

12. CONCLUSIONS.

Ideally, the path of reaction should be predicted from the contours on an energy surface drawn to represent the change in total energy with variation of all the independent parameters. This problem is too complex to be solved at the present time, and interest has to be centred on the alteration of the total energy with variation in single parameters or small groups of parameters, called factors.

Thus we have the " geometric factor " (Ballandin, *Z. physikal. Chem.*, 1929, *B*, **2**, 289; 1929, *B*, **3**, 167; *Acta Physicochim. U.R.S.S.*, 1941, **14**, 223; Beeck, *Review Mod. Physics*, 1945, **17**, 61; also a recent review by Griffiths in " Recent Advances in Catalysis," Vol. I, p. 91, Academic Press, Inc., New York) and the " electronic structure " factor (Roginsky and Schultz, *Z. physikal. Chem.*, 1928, *A*, **138**, 21; Russell, *Nature*, 1926, **117**, 47). These factors are obviously not independent and, from the point of view of convenience in practical application, that one is preferred which shows the sharpest change with variation in catalyst activity. The preferred factor is undoubtedly that of electronic structure inasmuch as it can be related to physical measurements such as magnetic susceptibility, electrical conductivity and related phenomena, dielectric constants, etc., even when the crystal parameters are unknown or the catalyst amorphous.

The semi-empirical theories advanced in the earlier sections have been used in our laboratories at Billingham since 1943 and have permitted, it is thought, a closer insight into methods of catalyst preparation and action than was obtainable on a purely geometric basis. These studies are being continued in order to strengthen the relatively weak theoretical bases, to provide a quantitative approach, and particularly to derive experimental support for the many deductions from theory. This continuation includes not only experiments in limited systems of high purity and exact definition, but also the amassing of empirical data over wider, more ambiguous systems where the pattern of results points with more generality, although less clarity, to the desired conclusion.

Finally, I must express my thanks to my associates, particularly to Dr. J. G. M. Bremner, for many helpful discussions.

IMPERIAL CHEMICAL INDUSTRIES (BILLINGHAM DIVISION),
BILLINGHAM, CO. DURHAM.

[*Received, October 14th, 1949.*]

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57. *Heterogeneous Catalysis. Part II. Hydrogenation by Binary Alloys.**

By PETER W. REYNOLDS.

The simple geometrical theory of catalytic activity is inadequate to explain the large difference in activity for hydrogenation between the metals of group 8 and those of group 1b. The alternative correlation of the catalytic activity with the electronic properties of the metal, discussed in Part I of this paper, associates the high activity of the group 8 metals with the holes in their 3*d*-, 4*d*-, and 5*d*-bands which are filled up in the metals of group 1b. By the examination of three series of nickel–copper catalysts it has been shown that the activity of the nickel declines in parallel with the filling of the holes in its 3*d*-band by the valency electrons of the copper, and that this occurs while the crystal lattice is expanding slightly in the direction of increased activity on the simple geometric view.

IT seems reasonable to believe that the interatomic spacings in the surface planes of solid catalysts must be closely related to the parameters of molecules which react upon them (see review by Griffith, " Advances in Catalysis," 1948, vol. I, p. 91). Beeck and his co-workers (Beeck, Smith, and Wheeler, *Proc. Roy. Soc.*, *A*, 1940, **177**, 62) added considerable weight to this evidence by their work on the hydrogenation of ethylene over evaporated films of Group 8 metals. Random films of nickel, evaporated *in vacuo*, had only one-fifth of the specific activity of oriented films evaporated in a low pressure of an inert gas. The catalytically active surface was composed of spire-like prominences (Beeck and Rust, U.S.P. 2,223,777), so that the films were porous and the total surface and activity practically proportional to the weight of the deposit. In the oriented deposits the 110 planes of the nickel were parallel to the backing. In the absence of further evidence it does not seem necessary to conclude with these authors that the 110 planes were therefore preferentially exposed, but unless the presence of the inert gas had profoundly modified the structure of the metallic deposit the activity of the nickel must have been affected by its crystallographic orientation.

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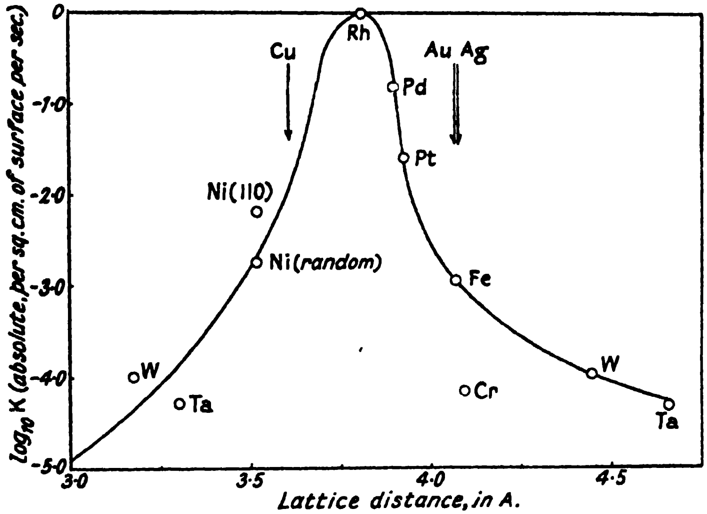
Following this indication Beeck (*Review Mod. Physics*, 1945, **17**, 61) has related the activity of metal catalysts in the hydrogenation of ethylene to their crystal parameters. His conclusions are reproduced in Fig. 1 where the logarithm of the reaction-velocity constant is plotted against the parameter of the metal. It is not always clear on what grounds this parameter has been selected from the alternatives available, but in the case of the face-centred cubic metals of Group 8 (nickel, rhodium, palladium, and platinum) it corresponds with the cell dimension.

FIG. 1.

Activity of metals in hydrogenation of ethylene v. *crystal parameter* (*Beeck*).



It seems probable that such spatial factors must play their part, but even if the suggested geometrical relations are necessary for high activity, they are certainly not sufficient. Thus copper, silver, and gold crystallise with a face-centred cubic lattice, and their parameters (Fig. 1) suggest high activities where in fact there is relatively little (copper) or practically none (silver and gold). Moreover it is always possible that these geometric correspondences are only incidental, and the prevalent tendency to hunt among the Miller indices for a plane with a promising spacing is viewed with suspicion.

In Part I of this paper an attempt was made to find alternative, more fundamental correlations between the catalytic activity and the physical structure of solids. In the simplest example of hydrogenation over metallic catalysts, the activity of Group 8 metals is attributed to the unfilled electron levels in their 3*d*-, 4*d*-, and 5*d*-bands. The relative inactivity of copper, silver, and gold is thus accounted for, because in these metals those bands are filled. Moreover, it is to be expected that any factor which tends to fill up the *d*-bands in Group 8 metals will result in a corresponding decrease in their activity.

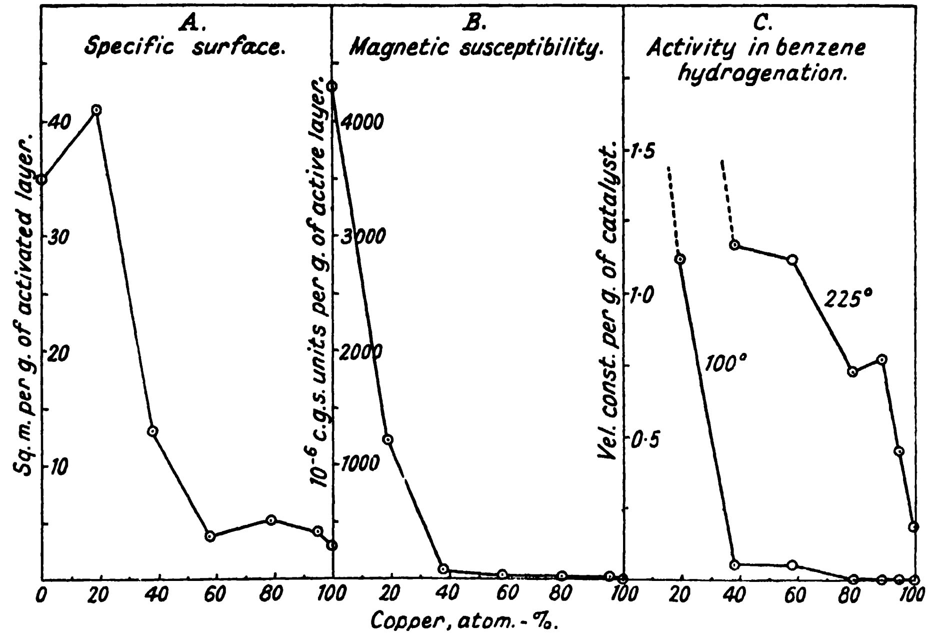
It is therefore of particular interest to study the physical and catalytic properties of the binary alloys of Group 8 metals with one another and with the metals of Group 1b (copper, silver, and gold). Work on these systems is in progress in these laboratories. The principal effort is being directed to the study of spectroscopically-pure metallic foils, but results already obtained on industrial catalysts in the nickel–copper system support the theoretical picture given in Part I and are discussed below.

Nickel and copper both crystallise with a face-centred cubic lattice; the lattice constants are 3·517 and 3·608 A. respectively. There is a complete range of homogeneous solid solution in their binary alloys within which the crystal parameter varies almost linearly with the atomic composition (Owen and Pickup, *Z. Krist.*, 1934, **88**, 116). Beeck's correlation suggests an increase in the specific activity of nickel by the inclusion of copper which expands the lattice. The electronic picture, on the other hand, suggests a marked fall in the activity of the nickel as the valency electrons of the added copper fill the holes in its 3*d*-band. In pure alloys at equilibrium these holes are just filled by the addition of about 60 atom-% of copper. The ferromagnetism, as measured by the large magnetic susceptibility at a fixed field strength, diminishes very rapidly at about the same composition (Kaufmann and Starr, *Phys. Review*, 1943, **63**, 445).

Data in the literature on the properties of nickel–copper catalysts are inadequate. Dupont and Piganiol (*Bull. Soc. chim.*, 1939, [v], **6**, 322) studied the influence of contamination of Raney nickel by copper on its activity for the hydrogenation of *allo*ocimene; the activity per unit weight of nickel decreased approximately linearly with increasing copper content to a low value at 50% of copper. Rienäcker (see Himmler, F.I.A.T. Review of German Science, Physical Chemistry, 1939—46, p. 97) examined nickel–copper foils for the hydrogenation of ethylene and the dehydrogenation of formic acid, and reduced nickel–copper oxide for hydrogenation of cinnamic acid. In each case the activity–composition curve exhibited a sharp step down to the low activity of copper, but the positions of these steps in the two cases were widely different. The specific surfaces of the catalysts were not measured.

FIG. 2.

Properties of alloy-skeletal powder nickel–copper catalysts.

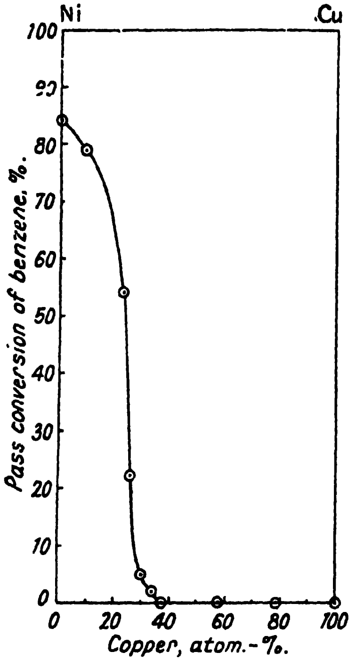


In the present work, two types of alloy-skeletal nickel–copper catalysts have been examined for hydrogenation of benzene, and reduced nickel–copper oxide on kieselguhr catalysts for hydrogenation of styrene. The specific surfaces and the magnetic susceptibilities of the catalysts were determined.

Powdered nickel–copper catalysts of the Raney type were prepared by exhaustive extraction of nickel–copper–aluminium alloy powders with aqueous sodium hydroxide. The results of specific surface and magnetic susceptibility measurements in arbitrary units are summarised in Fig. 2*A* and 2*B*, and their activities in the liquid-phase hydrogenation of sulphur-free benzene at 250 atmospheres are shown in Fig. 2*C*. The highly exothermal nature of the reaction made it impossible to determine the very high activity values for the pure nickel catalysts in the apparatus employed. This series of catalysts exhibited a marked fall in specific surface with increasing copper content until at 40% of copper the specific surface had fallen to 11% of the value for pure nickel. The activity at 100°, measured per unit weight of catalyst,

FIG. 3.

Activity of foraminate nickel–copper catalysts in benzene hydrogenation at 1 atm. and 100°.



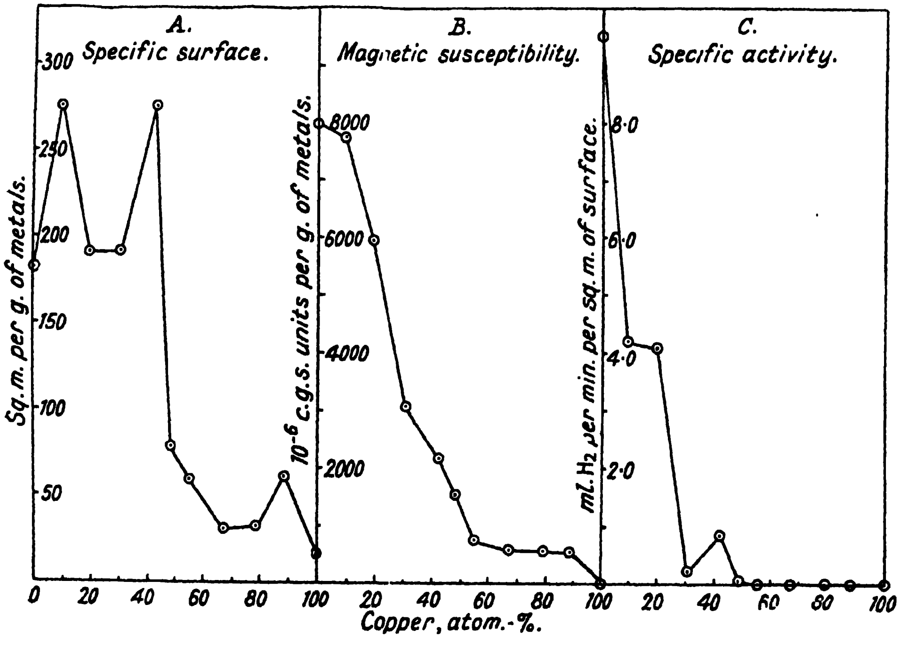
fell at a greater rate to a negligible value at the same composition. The fall in activity is thus greater than can be accounted for by the simultaneous drop in the specific surface, and it is noteworthy that it was at this composition also that the magnetic susceptibility at a fixed field strength fell to an insignificant value. Activity measurements at 225° followed the same trend, but these showed also a small decreasing residual activity at the higher copper contents, which presumably reflects the slight incompleteness of filling of the *d*-band indicated, even in alloys at equilibrium, by residual ferromagnetism at copper contents higher than the 60 atom-% where the *d*-band is ideally filled (Kaufmann and Starr, *loc. cit.*). A 100% copper catalyst prepared from spectroscopically pure metals had only one-fifth of the activity of that described above; this result suggests that an ideally pure copper catalyst would be inactive for hydrogenation of benzene. This conclusion is in line with the work of Ipatieff, Corson, and Kurbatov (*J. Physical Chem.*, 1939, **43**, 589) and of Morris and Selwood (*J. Amer. Chem. Soc.*, 1943, **65**, 2245).

Granular alloy-skeletal nickel–copper catalysts, prepared by surface activation of similar alloys, were tested in vapour-phase benzene hydrogenation at 100° at atmospheric pressure. The results are summarised in Fig. 3. Activity fell off rapidly as the copper content of the active nickel–copper layer increased from 20 to 30 atom-%; catalysts with 40 atom-% or more of copper were inactive. If it may be assumed that the specific surface and magnetic properties of the activated layer on the outside of these granules followed the same trends as in the powdered catalysts, then in this case also the specific activities disappeared with the large ferro-magnetism.

Reduced nickel–copper oxide on kieselguhr was examined in the liquid-phase hydrogenation

FIG. 4.

Properties of reduced-oxide nickel–copper catalysts.



of methanolic styrene at 30° and atmospheric pressure. The specific surface and magnetic susceptibility measurements at a fixed field strength are summarised in Fig. *4A* and *4B*, and the catalytic activities per unit area of active surface in Fig. *4C*.

There is thus in all these catalysts a parallel decline in specific activity and magnetic susceptibility at a fixed field strength as the content of copper is increased. The values of both become very small or zero at 30—40 atom-% of copper in the alloy-skeletal catalysts and at 50—60 atom-% in the reduced oxide catalysts. The occurrence of the critical composition at values below the 60 atom-% which would have been expected from the properties of the pure alloys at equilibrium is undoubtedly caused by the complexity of these actual catalysts. Yet the results do show that the catalytic activity of nickel falls away in parallel with the filling of its *d*-band holes by the valency electrons of the copper, and that this occurs while the lattice is expanding in the direction of increased activity on the simple geometric view.

EXPERIMENTAL.

Alloy-skeletal Catalysts.—Alloy melts were prepared in graphite crucibles from Mond nickel pellets, electrolytic copper of greater than 99·99% purity, and virgin aluminium of greater than 99·5% purity. All the alloys were made to contain 50% by weight of aluminium, except those for the pure nickel and pure copper catalysts which contained 58 and 45% by weight of aluminium respectively. The homogeneous melts were chill-cast on to copper moulds, and the cooled slabs crushed and screened. Granules of approx. 1/8″ diameter were selected for the foraminate catalysts, and the remaining material was ground to pass a 200 B.S. sieve mesh. (Alloy-skeletal catalysts in robust granular form, prepared by surface extraction of alloy granules, are termed " foraminates " in contradistinction to the Raney-type catalysts which are in powder form. Aluminium extraction in the latter is nearly complete.) These alloys were prepared by Messrs. Murex Ltd., Rainham, Essex.

For the Raney-type catalysts, amounts of powder containing 5 g. of active metals were added during 5 minutes to 100 ml. of a mechanically stirred boiling 30% aqueous solution of sodium hydroxide. The mixture was digested for 30 minutes, the catalyst then allowed to cool and settle, and the clear liquid decanted from the sludge. The catalyst was then re-treated by boiling for 30 minutes with a further 100 ml. of 30% alkali. This liquor also was removed by decantation, and the catalyst washed by decantation with ten 500-ml. portions of distilled water at 40°, three 150-ml. portions of " refined dry " methanol, and finally with three 100-ml. portions of sulphur-free benzene. Care was taken at every stage to prevent loss of catalyst in the decantations. The activated powders were kept under benzene and used as soon as possible.

Foraminate catalysts were prepared from the same alloys by extracting the 1/8″ granules with 2% aqueous sodium hydroxide passed over them at 25 ml. per ml. of catalyst per hour at 100° until 20% of the original aluminium was removed. The progress of the extraction was followed by measuring the hydrogen evolved. The activated granules were then washed for 6 hours with cold distilled water at the same space velocity, stored under water, and used as rapidly as possible. These foraminates consisted of an activated alloy-skeletal surface layer on an unaltered alloy core.

Even the finely divided activated powders retained unextractable aluminium in their interior. The total residual aluminium in the activated 42 : 58 nickel–aluminium powder was only 2·4% and in the activated 55 : 45 copper–aluminium 6·3%. In the 20 : 30 : 50 nickel–copper–aluminium alloy, however, it was as high as 37·8%, and further extraction in molten sodium hydroxide did not greatly reduce these figures. Catalysts in the middle of the series must therefore be regarded rather as finely divided foraminates than as Raney powders, each little particle consisting of an activated surface on an unaltered alloy core. The extent of extraction was, however, more than sufficient to develop the maximum activity of the catalyst.

Reduced-oxide Catalysts.—The reduced-oxide nickel–copper on kieselguhr catalysts were prepared by precipitation from the mixed metallic nitrates. The materials taken in each case corresponded to 20% by weight of the mixed oxides on 80% of Johns Manville's " Celite 519-A." In each preparation 80 g. of iron-freed kieselguhr were suspended in 400 ml. of solution containing the requisite nickel and copper nitrates, and the metals salts were precipitated at room temperature by the stirred addition of a slight excess of solid ammonium hydrogen carbonate. The products were heated for 1 hour at 100° with stirring and then dried at 120° without filtration. The ammonium nitrate was decomposed and the basic carbonates of the metals converted into the oxides by cautious ignition in open dishes, followed by calcination for 4 hours at 400°. The powders were reduced for 4 hours at 500° in purified electrolytic hydrogen immediately before use.

Specific Surface.—The total specific surface areas of the powdered alloy-skeletal and reduced-oxide catalysts were measured by argon adsorption at the temperature of boiling liquid oxygen using the method of Brunauer, Emmett, and Teller. The results are given in Tables I and II. The areas of the powdered alloy-skeletal catalysts have been recalculated to refer to the active layer on the assumption that the whole of the residual aluminium is present in the unaltered alloy core, and these recalculated values are plotted in Fig. *2A*.

Specific-surface measurements were not attempted on the foraminate catalysts, but it is probably safe to assume that the specific surface of the activated layer on the 1/8″ granules varied with composition in the same manner as that on the particles passing a 200 B.S. mesh.

The extent of coverage of the kieselguhr in the reduced-oxide catalysts is unknown. The small contribution of the kieselguhr to the total surface has therefore been neglected in calculating the specific surface of the active metals. The area of the " Celite 519-A " used was 3·4 m.^{2} per g., so that its maximum contribution would correspond to 17 m.^{2} per g. of active metals. The incompleteness of reduction of the oxides has also been neglected in the calculations. The values are plotted in Fig. *4A*.

TABLE I.

Alloy-skeletal powder catalysts.

Alloy composition, % by wt.			Residual aluminium, %.	Atom-% of copper in activated layer.	Specific area.	
Ni.	Cu.	Al.			Sq. m. per g. of powder.	Sq. m. per g. of activated layer.
42	0	58	2·4	0	34	35
40	10	50	24·2	19	28	41
30	20	50	33·6	38	6·6	13
20	30	50	37·8	58	1·5	3·8
10	40	50	29·1	79	3·0	5·1
2·5	47·5	50	11·0	95	3·6	4·1
0	55	45	6·3	100	2·8	3·0

TABLE II.

Reduced-oxide-on-kieselguhr catalysts.

Analysis of material ignited at 400°.		Atom-% of Cu in reduced metals.	Specific area of reduced catalyst:	
Ni, % by wt.	Cu, % by wt.		$m.^2$/g. of catalyst.*	$m.^2$/g. of metals.
15·9	0·0	0·0	29	182
14·1	1·6	9·5	44	278
12·4	3·3	19·7	30	191
10·3	5·0	30·9	29	192
8·6	6·8	42·2	43	278
7·6	7·7	48·4	12	78
6·8	9·2	55·5	9·4	59
4·8	10·8	67·5	4·9	31
3·0	12·3	79·1	4·9	32
1·7	13·9	88·3	9·5	61
0·0	15·4	100·0	2·6	17

* Weighed before reduction.

TABLE III.

Magnetic susceptibilities (at 4000 Oersted) of alloy-skeletal powder catalysts.

	Magnetic susceptibility in 10^{-6} c.g.s. units:			Magnetic susceptibility in 10^{-6} c.g.s. units:	
Cu, atom-%.	per g. of catalyst.	per g. of active layer.	Cu, atom-%.	per g. of catalyst.	per g. of active layer.
0	4200	4300	79	23	39
19	830	1220	95	10	11
38	42	85	100	4	4
58	17	43			

TABLE IV.

Magnetic susceptibility (at 4000 Oersted) of reduced-oxide catalysts.

	Magnetic susceptibility in 10^{-6} c.g.s. units:			Magnetic susceptibility in 10^{-6} c.g.s. units:	
Cu, atom-%.	per g. of reduced catalyst.	per g. of active metals.	Cu, atom-%.	per g. of reduced catalyst.	per g. of active metals.
0·0	1280	8000	55·5	118	740
9·5	1140	7750	67·5	94	590
19·7	950	5950	79·1	90	560
30·9	490	3060	88·3	87	545
42·2	345	2160	100·0	0	0
48·4	244	1530			

Magnetic Susceptibility.—Magnetic susceptibilities were measured by a Sucksmith balance at a fixed field strength of 4000 Oersted. The susceptibilities of the unactivated nickel–copper–aluminium alloys were all very small, and they have been neglected in calculating the values given in Table III of the mass susceptibility per g. of active layer. The values for the reduced-oxide catalysts are given in Table IV. No measurements were made on the foraminate catalysts.

Alloy-skeletal Powder Catalysts in Liquid-phase Hydrogenation of Benzene.—Liquid-phase hydrogenation of benzene was carried out in a 250 ml. stainless steel Lindsay–Baskerville autoclave, which had been modified to prevent catalysts from being splashed into the upper parts of the stirrer mechanism and lagged to give reasonable uniformity of temperature in the reaction vessel. An internal thermocouple was also fitted.

Alloy-skeletal powders prepared, as already described, from 5-g. portions of alloy were charged with 75 ml. of an equimolar mixture of sulphur-free benzene and sulphur-free *cyclo*hexane. The apparatus was assembled, pressure-tested under nitrogen, and heated to the reaction temperature under

5 atm. of nitrogen (measured at 20°). The temperature was levelled out with the stirrer in operation, and the pressure made up to 250 atm. with electrolytic hydrogen. The rate of reaction was followed by the decreasing hydrogen pressure, and the activities of the catalysts are expressed in terms of the true rate constants (Fuzek and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 3743):

$$(2{\cdot}303\ V/mt) \log_{10} P_0/P \text{ (ml. per g. of catalyst per min.)}$$

where V = volume (ml.) of gas-filled space in reactor, m = weight (g.) of catalyst, P_0 = initial hydrogen pressure (atm.), and P = hydrogen pressure (atm.) after time t (min.).

With pure nickel, and the 19 atom-% copper catalyst at the higher temperature, the rate of reaction was so high that the temperature became uncontrollable; runs with reduced amounts of catalyst were unreliable. Results for the remaining catalysts at 100° and 225° are given in Table V. These results have been plotted in Fig. 2*C*. A catalyst prepared from copper and aluminium which were both of spectroscopic purity was also tested; the figures are included in the table.

TABLE V.

Liquid-phase hydrogenation of benzene over alloy-skeletal powders.

Copper in activated layer, atom-%.	Reaction velocity constants at 100°.	Reaction velocity constants at 225°.	Copper in activated layer, atom-%.	Reaction velocity constants at 100°.	Reaction velocity constants at 225°.
0	—	—	89	0·00	0·77
19	1·12	—	95	0·00	0·45
38	0·05	1·17	100	0·00	0·19
58	0·05	1·12			
79	0·00	0·73	100 (Spect. pure)	0·00	0·04

Foraminate Catalysts in Vapour-phase Hydrogenation of Benzene.—Vapour-phase hydrogenation of benzene was effected with an equimolar mixture of sulphur-free benzene and sulphur-free *cyclo*hexane fed at a total liquid space velocity of 10 hr.$^{-1}$ over 10 ml. of the foraminate catalyst maintained at 100°. The hydrogen rate was 60 l. per hour. Activities were estimated in terms of the mean pass conversion of the benzene calculated over 2-hour runs. The results are given in Table VI and plotted in Fig. 3.

TABLE VI.

Vapour-phase hydrogenation of benzene over foraminate catalysts.

Copper in active layer, atom-% ...	0	9	23	26	30	34	38	58	79	100
Pass conversion of benzene, % ...	84	79	54	22	5	2	0	0	0	0

Reduced-oxide Catalysts in Liquid-phase Hydrogenation of Styrene.—A 10% solution of redistilled styrene in "refined dry" methanol was hydrogenated at atmospheric pressure in a 100-ml. glass shaker tube immersed in a thermostat at 25°. Electrolytic hydrogen was further purified by passage through active charcoal cooled in liquid oxygen; its rate of absorption in the reactor was measured by a soap-film flowmeter. The rate of reaction was found to be independent of the styrene concentration and approximately proportional to the weight of the catalyst.

The reaction vessel was equipped with a ground-glass joint at the top and with an alternative head carrying inlet and outlet gas leads for catalyst reduction. In each experiment 0·1 g. of supported oxide was charged to the reaction vessel on its side, spread over the wall, and reduced for 4 hours at 500°. The catalyst was cooled under hydrogen, immersed in acceptor solution, and transferred in the reactor to the test apparatus. The charge was there quickly frozen by cooling it in liquid oxygen, the apparatus evacuated, and hydrogen admitted. The reaction mixture was then allowed to warm to 25° in a thermostat, and vigorously agitated by a Microid shaker.

The results are given in Table VII. The activities are recorded first as ml. of hydrogen (at 20°/760 mm.) absorbed per minute per g. of active metals, and then in terms of unit area of active metal surface by the use of the figures of Table II. The latter results are plotted in Fig. 4*C*.

TABLE VII.

Liquid-phase hydrogenation of styrene over reduced-oxide catalysts.

Copper in reduced metals, atom-%.	Catalytic activity in ml. of H_2 absorbed per min. per g. of active metals.	Catalytic activity in ml. of H_2 absorbed per min. per sq. m. of active surface.	Copper in reduced metals, atom-%.	Catalytic activity in ml. of H_2 absorbed per min. per g. of active metals.	Catalytic activity in ml. of H_2 absorbed per min. per sq. m. of active surface.
0·0	1730	9·5	42·2	235	0·84
9·5	1170	4·2	48·4	0·5	0·006
19·7	790	4·1	55·5, 67·5, 79·1, 88·3, 100·0	0·0	0·000
30·9	46	0·24			

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IMPERIAL CHEMICAL INDUSTRIES LTD.,
RESEARCH DEPARTMENT, BILLINGHAM, CO. DURHAM.

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58. *The Heats of Hydrolysis of the Chloro-substituted Acetyl Chlorides.*

By H. O. Pritchard and H. A. Skinner.

From measurements of the heats of hydrolysis of $CH_3·COCl$, $CH_2Cl·COCl$, $CHCl_2·COCl$, and $CCl_3·COCl$ in aqueous-acetone solution, the following values (kcals. mole^{-1}) were obtained for the respective heats of formation (Q_f) of the liquids at room temperature: 66·2, 70·1, 68·7, and 68·8.

In an earlier communication, Carson and Skinner (*J.*, 1949, 936) reported some new measurements on the heats of hydrolysis of the acetyl halides. The present work is an extension of these studies to mono-, di-, and tri-chloroacetyl chlorides. Only one reference exists in the literature to previous measurements on the heats of hydrolysis of this group of compounds, in which Rivals (*Ann. Chim. Phys.*, 1897, **7**, 541) quoted values for the hydrolysis heats of mono- and tri-chloroacetyl chloride. The heat of hydrolysis of dichloroacetyl chloride does not seem to have been measured before.

Whereas acetyl chloride reacts very rapidly with water at room temperature, the chloro-substituted acetyl chlorides hydrolyse slowly, owing to their slow rate of dissolution in water. In aqueous acetone, on the other hand, the compounds hydrolyse quite rapidly, and we have found it convenient to use an aqueous acetone solvent in most of the present investigations.

Experimental.

Preparation of Compounds.—Chloroacetyl chloride was a B.D.H. product, purified by careful fractionation in a Fenske packed column; b. p. 105·4—105·5°/763 mm. The product was further purified by bulb-to-bulb distillation in a vacuum, and the pure fractions were collected and sealed in weighed glass ampoules.

Dichloroacetyl chloride was a B.D.H. product, purified in an exactly analogous manner; b. p. 107·0—107·4°/761 mm. The purified commercial sample was found on analysis to contain a small amount (0·03%) of sulphur (presumably from the thionyl chloride used in its preparation). As a check on the results obtained with the commercial sample, a further sample of dichloroacetyl chloride was prepared from dichloroacetic acid and benzoyl chloride (Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325), and carefully purified by fractionation in a Fenske column operating at a high reflux ratio: b. p. 107·7—107·8°/767 mm.

Trichloroacetyl chloride was prepared according to Leimu's method (*Ber.*, 1937, **70**, 1040) by the action of thionyl chloride on trichloroacetic acid in benzene solution. The crude product was fractionated in a Fenske column, and later distilled *in vacuo* and sealed in weighed glass ampoules.

Calorimeter.—The reactions were carried out by breaking thin glass ampoules containing a known amount of the acid chloride into a large excess of water, or aqueous acetone. The reaction vessel was a silvered Dewar flask (1 l. capacity), with a single narrow neck (1¼" diameter). The neck was closed with a polystyrene stopper which, in turn, was covered by a heavy close-fitting brass cap. A glass rotary propeller stirrer (100 r.p.m.) fitted centrally through the cap and stopper. Two additional holes through the stopper carried an electrical heater (for calibration purposes), and the resistance thermometer and leads. A circular brass plate, supported by two thin brass rods from the under side of the polystyrene stopper, served as a bottom bearing for the stirrer, and also for breaking the glass ampoules which could be depressed at any desired moment on to a cluster of spikes on one side of the plate. All the metal parts inside the calorimeter were rhodium-plated.

The Dewar vessel was submerged and supported in an accuratedly thermostated oil-bath, which, together with all the accompanying electrical apparatus, was kept in a thermostated room. The thermostat bath was a rectangular glass tank (15" × 12") fitted to a depth of 12" with white mineral oil. The bath was heated with mat heaters mounted about ½" off the bottom, and was efficiently stirred by a 10" four-bladed propeller driven by a flexible drive from outside the bath. The temperature control was maintained at 21° by a toluene regulator (extending through the bath). A Gouy head (Sligh, *J. Amer. Chem. Soc.*, 1920, **42**, 60) was used with the toluene regulator. The whole calorimeter assembly was essentially a modification of that used by Williams (*ibid.*, 1942, **64**, 1395).

The calibration heater was layer wound from 35 S.W.G. silk-covered Eureka wire on a 3-mm. ebonite rod to form an element 25 mm. in length (resistance 65 Ω). The heater was impregnated with cellulose acetate and encased in a platinum cylinder sealed to the end of a glass tube.

The resistance thermometer was a "Stantel" Thermistor (F 2311/300), and was carefully and rigidly mounted inside a thin glass tube, so that the tip was protected from external shock or pressure changes (Herington and Handley, *J. Sci. Instr.*, 1948, **25**, 434). Its resistance was measured to 0·05 Ω on a Cambridge glazed bridge in conjunction with a short-period reflecting galvanometer. The sensitivity of the resistance measurement is limited by the maximum continuous current rating of the thermistor: for the purpose of temperature measurement, this should not exceed 0·4 milliamp. The sensitivity under these conditions, with an optical lever of 1 metre, is *ca.* 1 Ω/cm.

Over small ranges of temperature, the temperature–resistance relation for a thermistor is of the form $T = k \log R$ (Becker, Green, and Pearson, *Trans. Amer. Inst. Elect. Eng.*, 1946, **65**, 711). By measuring the initial and final resistance of the thermistor (*i.e.*, R_i and R_f) over the course of an experiment, the heat change (Q) can be obtained from $Q = K \log R_i/R_f$, where K is a constant that includes the water equivalent of the system and the thermistor constant k. The constant K can be determined by passing a measured amount of electrical energy through the calibration heater (*e.g.*, see McInnes and Braham, *J. Amer. Chem. Soc.*, 1917, **39**, 2110) so as to obtain a change in the thermistor resistance comparable with that observed in an average experiment.

In general, a resistance change of 50—60 Ω (corresponding to a temperature change of *ca.* 0·75°) was aimed at in each experiment, so that we were able to measure the temperature changes to an accuracy of the order of 0·002°. We have found that the thermistor element gives reproducible results over long periods of time, and can successfully replace a Beckmann thermometer or other more conventional temperature-recording instrument, provided that due care is exercised in keeping the element free from strain.

Heats of Hydrolysis.—The preliminary investigation were carried out on chloroacetyl chloride, which is representative of a number of acid chlorides that react slowly with water at room temperature. Ampoules containing about 3 g. of the acid chloride were broken under 750 c.c. of water. The hydrolysis required about 2 hours to reach completion. Since an accurate estimation of the heat leakages over such a long time period is difficult, we sought to attain a faster reaction by using an equivalent amount of sodium hydroxide solution as the hydrolysing agent (see Rivals, *loc. cit.*), but found no marked increase in the rate of hydrolysis by this change in solvent. However, by using aqueous acetone as the hydrolysis medium, the rate of reaction was much increased, and the reaction times were reduced to 10 minutes with a solvent medium of 150 c.c. of acetone in 600 c.c. of water. The heats of hydrolysis observed in this solvent ($Q_{obs.}$) are convertible into hydrolysis heats in a purely aqueous medium ($Q_{aq.}$) by making small corrections for the difference in the heats of solution of the reaction products in the two solvents. These solution heat corrections (amounting to about 1 kcal. mole^{-1}) were measured as required, the most important of them being the heats of solution of the chloroacetic acids, which are roughly 1 kcal. mole^{-1} *less* in the above aqueous acetone than in pure water, as shown below :

Acid.	Solvent (mole-ratio)	$Q_{solution}$ (kcal. mole^{-1}).
$CH_3 \cdot CO_2H$ (liq.)	$700H_2O$	+0·34
	$(700H_2O + 35COMe_2)$	−0·42
$CH_2Cl \cdot CO_2H$ (crys.1)	$1100H_2O$	−3·30
	$(1100H_2O + 50COMe_2)$	−4·27
$CHCl_2 \cdot CO_2H$ (liq.)	$1350H_2O$	+2·67
	$(1350H_2O + 65COMe_2)$	+1·78
$CCl_3 \cdot CO_2H$ (liq.)	$1700H_2O$	+2·55
	$(1700H_2O + 80COMe_2)$	+1·70

Results.

Chloroacetyl Chloride.—The results obtained from five experiments on the hydrolysis of this chloride in *water* are given in Table 1(*a*), and from six experiments in the aqueous acetone solvent in Table I(*b*). The calculated values for Q_f ($CH_2Cl \cdot COCl$, liq.) given in the final columns of these tables are derived from the equation :

$$Q_f(CH_2Cl \cdot COCl) = Q_f(HCl,\ aq.) + Q_f(CH_2Cl \cdot CO_2H,\ aq.) - Q_f(H_2O,\ liq.) - Q_{aq.}$$

where the symbol Q_f is used to denote the heat of formation from the elements in standard states. The values for Q_f(HCl, aq.), Q_f($CH_2Cl \cdot CO_2H$, aq.) and Q_f(H_2O, liq.) were taken from the " Selected Tables of Chemical Thermodynamic Constants " (National Bureau of Standards, Washington, U.S.A.). The values found for Q_f($CH_2Cl \cdot COCl$, liq.) in Tables I(*a*) and I(*b*) agree reasonably well with each other, due

TABLE I.

Heat of hydrolysis of $CH_2Cl \cdot COCl$.

Expt.	Reaction mixture.	Wt. R·COCl (g.).	R_i (ohms).	R_f (ohms).	Q obs., kcals.	$Q_{aq.}$, kcals.	Q_f ($CH_2Cl \cdot COCl$, liq.), kcal. mole^{-1}.
			(a) *Hydrolysis in water.*				
1	R·COCl + $1300H_2O$	3·6086	1739·5	1678·6	—	22·56	69·91
2	R·COCl + $1520H_2O$	3·0950	1729·4	1677·6	—	22·44	70·04
3	R·COCl + $1590H_2O$	2·9464	1718·7	$1669{\cdot}3_5$	—	22·59	69·89
4	R·COCl + $1470H_2O$	3·1982	1735·1	1681·0	—	22·62	69·86
5	R·COCl + $1510H_2O$	3·1155	1737·9	1684·9	—	22·71	69·77
					Mean values	22·59	69·89
			(b) *Hydrolysis in aqueous acetone.*				
1	R·COCl + $(1280H_2O,$ $78COMe_2)$	2·9331	1707·8	1658·5	21·40	22·35	70·12
2	R·COCl + $(1190H_2O,$ $72COMe_2)$	3·1746	1745·0	1690·6	21·42	22·37	70·10
3	R·COCl + $(1320H_2O,$ $80COMe_2)$	2·8558	1743·5	1694·4	21·48	22·43	70·05
4	R·COCl + $(1220H_2O,$ $74COMe_2)$	3·0843	1725·7	1673·6	21·34	22·30	70·17
5	R·COCl + $(1270H_2O,$ $77COMe_2)$	2·9584	1742·7	1692·1	21·41	22·36	70·10
6	R·COCl + $(1630H_2O,$ $98COMe_2)$	2·3058	1744·1	1704·9	21·35	22·30	70·19
				Mean values	21·40	22·35	70·12

allowance being made for the tardiness of the aqueous hydrolysis, and the possible small errors involved in the correction terms required by the aqueous-acetone hydrolysis.

Dichloroacetyl Chloride.—The hydrolysis of dichloroacetyl chloride was studied in the aqueous acetone mixture, in which solvent the rate of hydrolysis is rapid, requiring about 10 minutes. Results from 6 experiments are presented in Table II. The data therein were obtained with the purified commercial dichloroacetyl chloride. Some check experiments using a sample prepared by Brown's method (*loc. cit.*) gave virtually identical results; *e.g.*, two experiments gave $Q_{obs.}$ = 24·84 and 24·83 kcals.

Trichloroacetyl Chloride.—The hydrolysis of this chloride was similarly studied in the aqueous acetone solvent, and, as previously, reaction times of *ca.* 10 minutes were found. The results are given in Table III.

TABLE II.

Dichloroacetyl chloride in aqueous acetone.

Expt.	Reaction mixture.	Wt. R·COCl (gs.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (kcals.).
1	R·COCl + (1150H_2O, 70$COMe_2$)	4·2658	1749·6	1684·8	24·80	25·67	68·78
2	R·COCl + (1380H_2O, 84$COMe_2$)	3·5676	1753·7	1699·1	24·85	25·72	68·75
3	R·COCl + (1240H_2O, 76$COMe_2$)	3·9763	1754·2	1693·7	24·74	25·61	68·86
4	R·COCl + (1240H_2O, 76$COMe_2$)	3·9815	1757·8	1696·5_5	24·97	25·84	68·63
5	R·COCl + (1255H_2O, 76$COMe_2$)	3·9272	1760·2_5	1700·0_8	24·84	25·71	68·76
6	R·COCl + (1265H_2O, 77$COMe_2$)	3·8989	1754·3	1694·5	24·93	25·80	68·68
				Mean values	24·86	25·73	68·74

TABLE III.

Trichloroacetyl chloride in aqueous acetone.

Expt.	Reaction mixture.	Wt. R·COCl (gs.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (kcals.).
1	R·COCl + (1400H_2O, 85$COMe_2$)	4·3432	1754·7	1695·7	27·27	28·10	68·84
2	R·COCl + (1300H_2O, 79$COMe_2$)	4·6746	1754·6	1691·3	27·22	28·05	68·87
3	R·COCl + (1300H_2O, 79$COMe_2$)	4·6771	1754·9	1691·2	27·37	28·20	68·72
4	R·COCl + (1275H_2O, 78$COMe_2$)	4·7666	1755·9	1691·3	27·23	28·06	68·86
5	R·COCl + (1225H_2O, 75$COMe_2$)	4·9530	1754·4	1687·0	27·39	28·22	68·69
				Mean values	27·30	28·12	68·80

TABLE IV.

Expt.	Reaction mixture.	Wt. R·COCl (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (kcals.).
		(a) *Acetyl chloride in water.*					
1	R·COCl + 1410H_2O	2·3207	1762·0	1705·8	—	22·17	66·15
2	R·COCl + 1380H_2O	2·3749	1760·6	1703·7	—	21·96	66·36
3	R·COCl + 1225H_2O	2·6734	1762·2	1697·3	—	22·28	66·03
4	R·COCl + 1290H_2O	2·5501	1762·4	1701·6	—	21·86	66·45
5	R·COCl + 1310H_2O	2·5025	1756·5	1696·4	—	22·09	66·22
6	R·COCl + 1280H_2O	2·5624	1747·4	1686·6	—	21·94	66·37
					Mean values	22·06	66·26
		(b) *Acetyl chloride in aqueous acetone.*					
1	R·COCl + (1060H_2O, 65$COMe_2$)	2·4652	1759·2	1698·3	21·34	22·08	66·22
2	R·COCl + (930H_2O, 57$COMe_2$)	2·8086	1757·5	1688·5	21·28	22·02	66·28
3	R·COCl + (1040H_2O, 63$COMe_2$)	2·5104	1758·5	1696·6	21·30	22·04	66·26
				Mean values	21·31	22·05	66·25

Acetyl Chloride.—As a check on the thermochemical method, we have remeasured the heat of hydrolysis of acetyl chloride, (*a*) in water and (*b*) in the aqueous-acetone solvent. As in the case of chloroacetyl chloride, the hydrolysis heat measured in the aqueous acetone ($Q_{obs.}$) was smaller than that measured in the purely aqueous solution ($Q_{aq.}$). After the necessary solution heat corrections had been made to $Q_{obs.}$, the derived $Q_{aq.}$ values agreed more or less exactly with one another. The results are summarised in Tables IV(*a*) and (IV(*b*). Compared with the results given earlier for acetyl chloride by Carson and Skinner (*loc. cit.*), there is a close correspondence in the observed heats of hydrolysis, but an apparent discrepancy in the values given for Q_f(CH_3·COCl, liq.). Part of the reason for this discrepancy lies in our use in this paper of the Q_f(CH_3·CO_2H, aq.) values recently recommended by the Bureau of Standards, Washington, but the main point of difference rests in an incorrect assumption by Carson and Skinner of a negligible heat of mixing of the aqueous hydrochloric and acetic acids in their experiments. We have since recalculated Q_f(CH_3·COCl, liq.) from the earlier data, making due allowance for the small mixing terms, and obtain Q_f(CH_3·COCl, liq.) = 66·0 ± 0·20 kcals. mole^{-1}. The agreement between the two sets of experimental data is thus seen to lie within the experimental error (*ca.* ±0·2 kcal.) of the two investigations.

DISCUSSION.

The results of the present investigation are summarised in the Q_f values listed below:

	Q_f (liq.) (kcals. mole^{-1}).	Q_f (gas) (kcals. mole^{-1}).	ΔQ_f.
$CH_3{\cdot}COCl$	66·2	59·4	+2·7
$CH_2Cl{\cdot}COCl$	70·1	62·1	−1·4
$CHCl_2{\cdot}COCl$	68·7	60·7	−0·2
$CCl_3{\cdot}COCl$	68·8	60·5	

The Q_f (gas) values are subject to some uncertainty, as data are not available for the heats of vaporisation ($\lambda_{vap.}$) of the chloroacetyl halides. We have estimated the $\lambda_{vap.}$ values by Trouton's rule, assuming the same value for Trouton's constant as obtains in acetyl chloride (Mathews and Fehlandt, *J. Amer. Chem. Soc.*, 1931, **53**, 3212), *viz.*, $\lambda_{vap.}$ ($CH_3{\cdot}COCl$) = 6·8 kcals. mole^{-1}.

The interesting feature of the above results lies in the *smallness* of the changes in Q_f arising from the successive replacement of each hydrogen atom in $CH_3{\cdot}COCl$ by chlorine atoms, and in the observed *fall* in Q_f in passing along the series $CH_2Cl{\cdot}COCl \longrightarrow CHCl_2{\cdot}COCl \longrightarrow CCl_3{\cdot}COCl$ (ΔQ_f values are negative). The increase in Q_f ($CH_2Cl{\cdot}COCl$) relative to Q_f ($CH_3{\cdot}COCl$) might be expected from analogy with other examples of chlorine substitution for which thermal data are available: *e.g.*,

	Q_f (kcals.).	ΔQ_f.
$CH_3{\cdot}CH_3$	20·2	+4·9
$CH_3{\cdot}CH_2Cl$	25·1	
$CH_3{\cdot}CH_2Cl$	25·1	+6·1
$CH_2Cl{\cdot}CH_2Cl$	31·2	
$CH_3{\cdot}CH_2{\cdot}OH$	56·2	+3·9
$CH_2Cl{\cdot}CH_2{\cdot}OH$	60·1	

	Q_f (kcals.).	ΔQ_f.
$CH_3{\cdot}CO_2H$ (liq.)	116·4	+3·2
$CH_2Cl{\cdot}CO_2H$ (liq.)	119·6	
CH_4	17·9	+1·7
CH_3Cl	19·6	

On the other hand, the negative values of ΔQ_f in passing from $CH_2Cl{\cdot}COCl$ to $CHCl_2{\cdot}COCl$, and from $CHCl_2{\cdot}COCl$ to $CCl_3{\cdot}COCl$, are perhaps surprising. In the case of, *e.g.*, the chloroacetic acids, the ΔQ_f (liq.) values, although small, remain positive:

$CH_3{\cdot}CO_2H$ (liq.)	116·4	+3·2
$CH_2Cl{\cdot}CO_2H$ (liq.)	119·6	+0·6
$CHCl_2{\cdot}CO_2H$ (liq.)	120·2	+1·2
$CCl_3{\cdot}CO_2H$ (liq.)	121·4	

but it may be that a genuine negative trend in ΔQ_f is masked by using the Q_f (liq.) values in place of Q_f(gas). At present, the negative ΔQ_f's of the chloroacetyl chlorides are unique among the rather scanty thermochemical data on chloro-substituted compounds. It should be borne in mind, however, that the Q_f values of the chloroacetyl chlorides depend on the values we have accepted for the heats of formation of the chloroacetic acids.

There is some independent evidence that the substitution of a second and a third chlorine atom into a methyl group leads to a smaller increment in Q_f than that brought about the substitution of the first chlorine atom: *e.g.*,

$CH_3{\cdot}CH_3$	20·2	+4·9
$CH_3{\cdot}CH_2Cl$	25·1	+3·9
$CH_3{\cdot}CHCl_2$	29·0	

Recently, Lacher, McKinley, Walden, Lea, and Park (*J. Amer. Chem. Soc.*, 1949, **71**, 1334) have given values for the heats of chlorination of a number of fluoro- and fluoro-chloro-substituted ethylenes, including:

$$CH_2{:}CH_2 + Cl_2 \longrightarrow CH_2Cl{\cdot}CH_2Cl + 43{\cdot}60 \text{ kcals.}$$
$$CF_2{:}CF_2 + Cl_2 \longrightarrow CF_2Cl{\cdot}CF_2Cl + 57{\cdot}32 \text{ kcals.}$$
$$CF_2{:}CCl_2 + Cl_2 \longrightarrow CF_2Cl{\cdot}CCl_3 + 41{\cdot}08 \text{ kcals.}$$

The data suggest that the C–Cl bonds in the groupings $-CF_2-Cl$, $-CH_2-Cl$, and $-CCl_2-Cl$ are not equal in strength, but vary in the order $-CF_2-Cl > -CH_2-Cl > -CCl_2-Cl$. This is compatible with (but not proof of) decreasing ΔQ_f with increasing chlorine substitution on the same carbon atom.

Relatively little is known of the heats of formation of the chloro-acetaldehydes, which form an analogous group of compounds to the chloroacetyl chlorides. The increment in Q_f in passing from CH_3·CHO to CCl_3·CHO, is, however, quite small (ΔQ_f = 3·3 kcals.). The corresponding increment in the series of acetyl chlorides, *viz.*, 1·1 kcals., is smaller still, which might suggest that the replacement of $^-$CHO by $^-$CClO gives rise to a more powerful steric repulsion between the relatively bulky chlorine atoms of the groups CCl_3 and CClO, than exists between the groups CCl_3 and CHO. It would be useful to have further data, particularly on the bromoacetyl halides, which should reveal steric repulsion effects in a more pronounced manner, if they indeed represent an important factor.

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59. *The Dielectric Polarisation of Gaseous Sulphur Dioxide.*

By R. J. W. LE FÈVRE, I. G. ROSS, and B. M. SMYTHE.

Two sets of measurements for the above property, over the temperature range 290—440° K., have been obtained independently and with non-identical apparatus. The two apparatus both possess the simplicity of, but incorporate improvements upon, the oscillator–wavemeter combination used before by Le Fèvre and Russell.

The total polarisation of sulphur dioxide is represented in c.c. by ${}_{T}P = 10{\cdot}91 + 16164/T$, whence the dipole moment is 1·619 D., and the atomic polarisation *ca.* 1·4 c.c. (or 15% of the electronic polarisation).

THE work now to be described was undertaken for two reasons : (*a*) because sulphur dioxide, being one of the simplest substances having a negative Kerr constant, seemed an attractive case upon which to test various extant " rules " for the variation of apparent dipole moment with state (cf. Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374, and following paper), and (*b*) because a need was felt, during day-to-day observations of dielectric constant (ε) on gases, for a reference compound having a higher value of ε than that of carbon dioxide, the material previously used (*idem, loc. cit.*). The remainder of this communication deals with point (*b*).

Sulphur dioxide, being readily available and easy to handle and purify, was an obvious choice as the desired secondary standard. Its earlier examination by Jona (*Physikal. Z.*, 1919, **20**, 14) and Zahn (*Physical Rev.*, 1926, **27**, 455) suggested that it would have advantages over carbon dioxide in that, for it, $\varepsilon - 1$ is about nine times as great, at room temperature. Consequently the change of capacity (*i.e.*, the quantity actually measured) following the introduction of sulphur dioxide between the plates of a condenser would be ten times that produced by carbon dioxide under equivalent conditions. As calibrating materials, therefore, these two gases should lead to accuracies, other things being equal, in much the same ratio.

Our plan, accordingly, has been to make a careful comparison of sulphur dioxide with carbon dioxide, using for the latter the dielectric constant of 1·000905 at 25° and 760 mm. (corresponding to a temperature-invariant polarisation of 7·341 c.c.) adopted by Le Fèvre and Russell (*loc. cit.*).

APPARATUS.

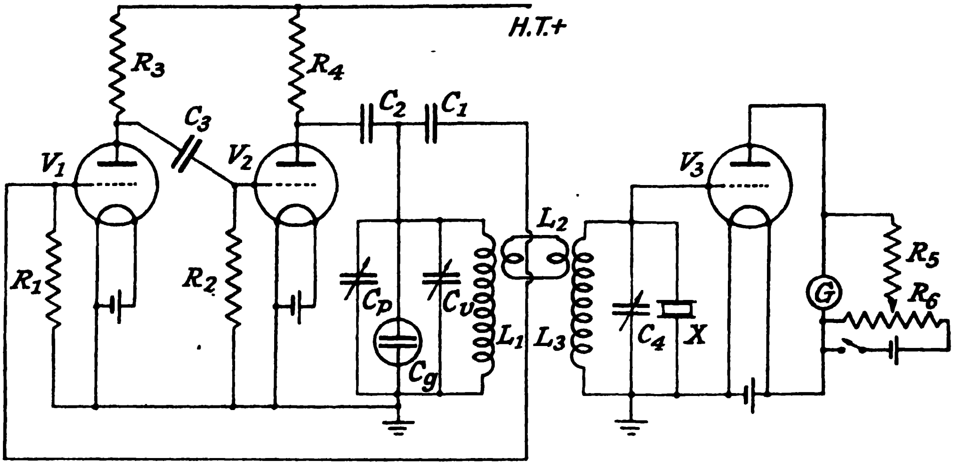
Le Fèvre and Russell (*loc. cit.*) had incorporated the replaceable capacity (gas cell) into the circuit of a dynatron oscillator, the signal from which was picked up in an adjacent wavemeter. Very little of their original apparatus, however, being available in Sydney, it became necessary to rebuild *de novo.* Certain facts then emerged which caused us to discard the dynatron. Since this generator is still recommended in the second edition of " Dipole Moments " (Methuen, 1948) we wish to state briefly our reasons for the change. (*a*) The secondary emission from the plates of modern valves is less easy to induce than was the case with those commercially obtainable eleven years ago; we observed this empirically ourselves and later learned that changes in manufacture and design have been deliberately directed to this end (private communication from Messrs. Amalgamated Wireless, Australia Ltd.). (*b*) Supposedly identical valves can have secondary-emission characteristics which vary over wide limits. " Samples which are closely uniform when used as amplifiers display marked disparity in dynatron characteristics. The dynatron effect is more or less accidental, and consistency is not always sought for " (Scroggie, *Wireless Eng. and Expt. Wireless*, 1933, **10**, 527). (*c*) We found unexpectedly that the available inductance : capacity ratios were limited by the fact that oscillations ceased when $-L/CR$ was made less than $(R_n)_{\text{minimum}}$ (R = resistance in the tank circuit, R_n = effective negative resistance of the valve, cf. Brunetti, *Proc. Inst. Radio Eng.*, 1937, **25**, 1595); the last point was a serious drawback since any factor tending to diminish the capacity of the gas cell would obviously react similarly upon the accuracy of our readings.

An experimental survey of other possible arrangements was therefore undertaken. These included variants of the heterodyne-beat method involving either audible or cathode-ray-tube reading-points. Several designs of oscillators were tried, mutually in pairs, or singly against the 50-c./s. mains or the carrier wave of a local Sydney broadcasting station. Finally we convinced ourselves that, except through a great increase of complexity (compare the circuit diagram of Stranathan, *Rev. Sci. Instr.*, **1934**, **5**, 334) and of associated maintenance troubles, no significant improvement would be secured over the very simple equipment used by Le Fèvre and Russell. The problem was thus reduced to choosing a variable oscillator to replace the dynatron.

Eventually we adopted (*a*) a push–pull circuit of the Franklin type, and (*b*) a transconductance generator, both using power supplies drawn entirely from batteries. These, each with an attendant wavemeter containing a quartz resonator, have formed the basis of two apparatus, built and operated separately and independently (by I. G. R. and B. M. S. respectively). They will now be described *seriatim*.

Franklin Oscillator–Wavemeter Combination (*see Fig.* 1).—The lay-out comprises a Franklin oscillator *A* (cf. Witt and Franklin, B.P. 369,575) coupled to a wavemeter *B*. The specifications of the circuit components are as follows. Valves V_1, V_2, V_3 : Radiotron 1H4-G. Capacitors : C_g, gas cell (described below); C_v, coarse variable condenser (second-grade Sullivan, maximum capacitance 200 pF.); C_p, precision variable condenser (see below); C_1 and C_2 should be equal and as small as possible, compatibly with adequate signal strength—7pF. was found to be satisfactory; C_3, 0·001 μF.; C_4, split-stator variable condenser, maximum capacitance 150 pF. Resistors : R_1, R_2, R_3, R_4, all 50,000 ohms; R_5, 20,000 ohms; R_6, 1000-ohms potentiometer. Inductances : L_1, 90 turns 20 S.W.G. cotton-covered copper wire wound on a hexagonal bakelite former, 1¼″ diameter, the whole coated with paraffin wax; L_3, 120 turns on a similar former; L_2, coupling coil, consisting of a single turn of stiff tinned copper wire, and located immediately above L_1, L_3, whose centres are 4½″ apart. *X*, quartz resonator crystal, frequency 1000 kc./s. (supplied in mount by Amalgamated Wireless, Australia, Ltd.); *G*, Cambridge galvanometer, sensitivity 1100 mm./microamp. at 1 m. The two circuits are built on separate steel chassis. C_g, C_v, and C_p are connected to the chassis by short lengths of coaxial cable.

FIG. 1.



(A) (B)

Gas Cell.—The gas cell C_g resembles that described by Le Fèvre and Russell. Three coaxial rhodium-plated brass cylinders (16 gauge) are separated by small rectangular quartz spacers, 12 in all, the inner and outer cylinders (each 10 cm. long and earthed) being connected by a ring fitting tightly between them; the H.T. lead is led out, from the middle cylinder (9 cm. long), through a hole in the ring *via* a glass bush. The cell is sealed into an annular " Pyrex " glass cylindrical vessel, provided with a gas inlet. The leads are of 26 S.W.G. platinum wire, and penetrate the top of the vessel to the lower ends of mercury-filled glass tubes, into which dip the connections to the oscillator. The empty capacity is roughly 200 pF. The high-tension electrode is shielded by a brass foil wrapping (earthed).

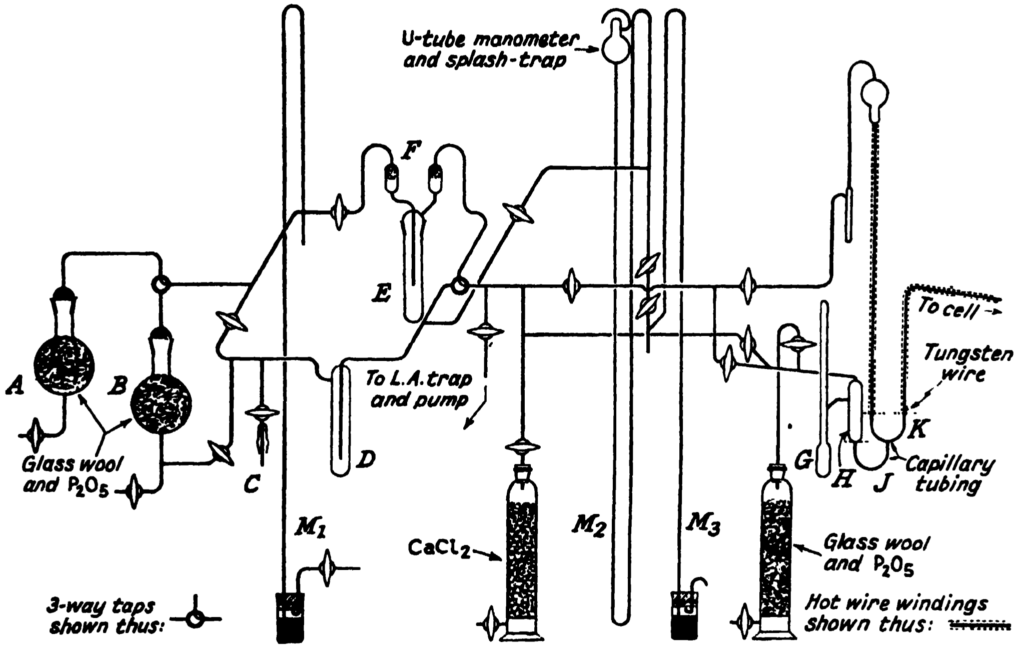
The cell is located by a brass-rod scaffolding in an oil-thermostat. The temperature is read from a calibrated thermometer placed in a symmetrical position to the cell with respect to the heaters and stirrer. The electrical components, including batteries and excepting only the gas cell and precision condenser, are enclosed in a large heavily-lagged box, lined with sheet zinc (earthed) for shielding. No thermostatic control has been found necessary.

Precision Variable Condenser.—The design of the precision condenser is substantially the same as that shown in Fig. 4. The steps have diameters of 3 cm. and 2·45 cm., the cylinder around them is 20 cm. long and of 2·375 cm. inner radius. The working range is 8 pF. traversed in 160 turns; each division (1/100th turn) then corresponds to 0·0005 pF. The limit of reading (set by the response of *G*) is one-half of such a division. The total capacity is about 35 pF.

Performance of Oscillator.—The frequency stability of the oscillator was beyond expectations. After it had run continuously for a fortnight, it was determined that, with C_g at room temperature, under conditions in which a change of frequency of ½ c./s. could be detected, no change was observed during ½ hour.

Performance of this kind is remarkable. It would be of interest to obtain an explicit expression for the frequency in terms of all the circuit components, so that the probable influence of the more likely sources of frequency drift could be accounted for. However, the theoretical and practical aspects of this particular oscillator have been virtually neglected in the literature. An attempt to apply Kirchhoff's laws to the equivalent circuit of the oscillator, along the lines followed by Llewellyn (*Proc. Inst. Radio Eng.*, 1931, **19**, 2063) for several simpler oscillators leads to excessively involved expressions, which, in any event, must be regarded as only approximate in view of his tacit neglect of phase changes in the process of amplification (cf. Jen, *ibid.*, p. 2109). None the less, it seems clear that the chief reason for the observed stability is the small coupling, provided by the condensers C_1, C_2, between the tank and the rest of the circuit. The whole can be regarded as an LC circuit, the capacitative arm, C, of which is shunted by (*a*) one of the coupling condensers, C_1 or C_2, and (*b*) the other coupling condenser (C_1 and C_2 may be considered as approximately equal) in series with an impedance, Z, representing the remainder of the circuit. Then, to the extent that C_1 or C_2 is negligible compared with C (or $C + C_{1 \text{ or } 2}$) it is justifiable to take the impedance of this arm as that of C alone, *viz.*, $1/j\omega c$, which is not influenced by changes of Z.

FIG. 2.



Resonance Curve.—The form of the resonance curve is not that shown in the paper of Le Fèvre and Russell (*loc. cit.*). Because the coupling of the circuits exceeds the critical value, the curve has two humps, with two major crevasses (on either of which readings can be taken), and upwards of 30 minor crevasses, all excessively sharp and narrow, and too sensitive for use; these may be due to the excitation of subsidiary modes of vibration of the crystal.

The maximum anode current in the wavemeter is about 60 microamps. Since the galvanometer used gives its full deflection with about 1 microamp., a balacing e.m.f. is applied. The arrangement shown in Fig. 1 is one which, unlike a simple series arrangement of cell and rheostat, gives a uniform increase in back current as the knob of the potentiometer R_6 is turned.

Coaxial Cable Effect.—It has been mentioned that the condensers C_g, C_p, C_v are connected to the chassis by coaxial cables. The important observation was made that the lengths of these cables influence strongly the amplitude of the resonance curve, as measured in the wavemeter circuit. In particular, if the length of cable connecting the cell (which constitutes the major part of the total capacity of the tank) to the rest of the circuit is doubled, the amplitude of the resonance curve is decreased by 30%. The effect of changing the lengths of cable to the smaller capacitances C_p and C_v is much less; while the connection of, say, one metre of unterminated cable in parallel with the other capacitances has no significant effect on the amplitude.

These considerations have a bearing on the design of the whole apparatus: to obtain maximum sensitivity it is necessary that the oscillator should be located as near as possible to the cell C_g.

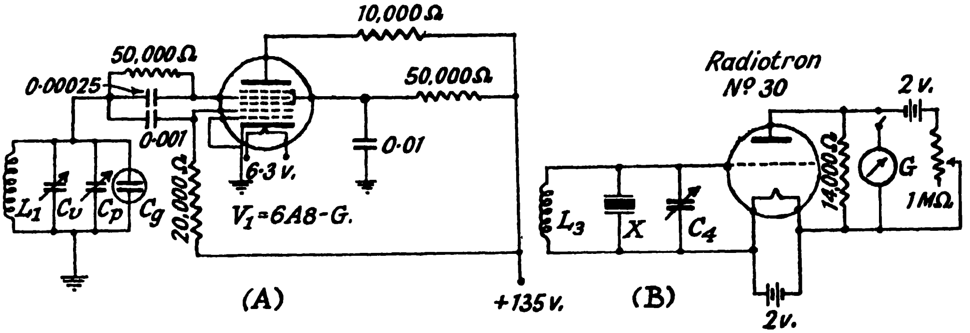
It is not known whether they have been noted with other oscillators. Their explanation is difficult. The most obvious suggestion is that power dissipation in the cable causes the drop in signal strength; for as the capacitance across the end of the cable is increased, so also the admittance of the cable + capacitance as a whole increases, and consequently also the power dissipated. It is uncertain just how the amplitude of oscillations depends on the effective resistance of the tuned circuit, although this is clearly a participating factor.

Significant losses in short lengths of high-quality cable are, however, unheard of. The cable used is A.W.A. Telcon h.f. cable, solid copper core (0·035″ diam.), with braided outer conductor (0·25″ diam.). The dielectric is a polythene–polyvinyl ester mixture, $\varepsilon = 2{\cdot}3$, resistivity 10^{17} ohm/cm., power factor 0·0003. The characteristic impedance, Z_0, is 70 ohms (modulus)—the calculated value is $75 + 1{\cdot}6j$ ohms —and the capacitance 21·5 pF./ft. The attenuation is 0·41 decibels/100 feet at 1 mc./s. (*i.e.*, for a correctly terminated line). Several different specimens of cable were used, and the connectors frequently refitted. The lengths of cable used (not more than 60 cm.) are no significant submultiple of a wavelength at 1 mc./s.

Using the appropriate exact transmission-line formulæ (Race and Larrick, *Trans. Amer. Inst. Elect. Eng.*, 1942, **51**, 526), the impedance of a cable of these specifications, 100 cm. in length, terminated by a capacitance of 500 pF., is found to be $1{\cdot}8—277j$ ohms, the real (resistive) part of which seems far too small to account for the effect described.

Gas-handling Apparatus.—The final form of the gas-handling apparatus is shown diagrammatically in Fig. 2. The bulbs, *A* and *B*, contain phosphoric oxide dispersed on glass wool, to serve for the preliminary drying of the gases. The connection of the traps (*E*, *D*) is such as to permit repeated cyclic distillation of gases. Of these traps, *E* is removable, and can thus be partly filled with drying agents, distillation over phosphoric oxide having been found the most effective method of drying. The bulbs, *F*, containing plugs of glass wool, serve to prevent phosphoric oxide being carried through the rest of the system when the liquid in the trap bumps while boiling. When blocked, the traps are cut out and replaced after washing.

FIG. 3.



The various connections to manometers enable a check to be kept on the pressures in all parts of the apparatus while distillation is in progress—a necessary precaution when icing of the downpipes of the traps occurs, with possible building up of back-pressures during distillation. M_2 is a U-tube manometer for working at positive pressures, and is equipped with a splash-trap.

The system to the right of M_2 is the device used by Groves and Sugden (*J.*, 1934, 1094; 1939, 1144, 1147). (Although not needed for sulphur dioxide, it was introduced during construction to allow higher-boiling liquids to be examined later, if desired.) The two gases are from cylinders. As a routine, they are dried (P_2O_5) and redistilled before admission to the cell.

Reading Procedure.—The oscillator and thermostat are allowed to run for about ½ hour to attain equilibrium. Two points on opposite sides of the bottom of the crevasse, about 14 condenser turns apart, and for which the galvanometer deflection is about 1 cm. per condenser scale-division, are used as reference points. Apart from the fact that during the taking of readings the heaters and stirrer in the thermostat are best switched off—since they cause slight instability—the sequence of operations is similar to that noted later (p. 280). Each set of readings takes approximately 12 minutes to perform.

Negative Transconductance Oscillator–Wavemeter Combination (*see Fig.* 3).—The oscillator (*A*) is built around a 6A8G Radiatron pentode, the three condensers C_v, C_p, and C_g being in parallel with the inductance L_1 (a ceramic grooved coil, 2″ in diameter, wound with 54 turns of No. 20-gauge bare tinned wire). The variable condenser C_v is a short-wave radio commercial type of *ca.* 100 pF., used to set the frequency of the oscillator approximately to that of the quartz (so that the plate current of the wavemeter is on the crevasse, and fine tuning then possible with the precision condenser C_p). C_v remains unaltered during a series of measurements. Resistors and other capacities are specified on Fig. 3. The wavemeter (*B*) is mounted on the same chassis as the oscillator, and the whole, with associated power supplies, housed in an insulated box to maintain fairly constant ambient temperatures around the components and to prevent radiation from the heated thermostat standing alongside.

Gas Cell.—This is simpler than that used by I.G.R., consisting of two brass tubes 9·5 cm. long, the inner of which (diameter, 5·1 cm.) is mounted concentrically with the outer (diameter 5·4 cm.). Six "Pyrex"-bead spaces, inserted under slight tension, prevent movement of the two cylinders. The assembly is sealed into an annular "Pyrex" envelope with the same kind of electrical connections as for the cell previously described. The outside cylinder is earthed. The empty capacity of this cell is approx. 80 pF.

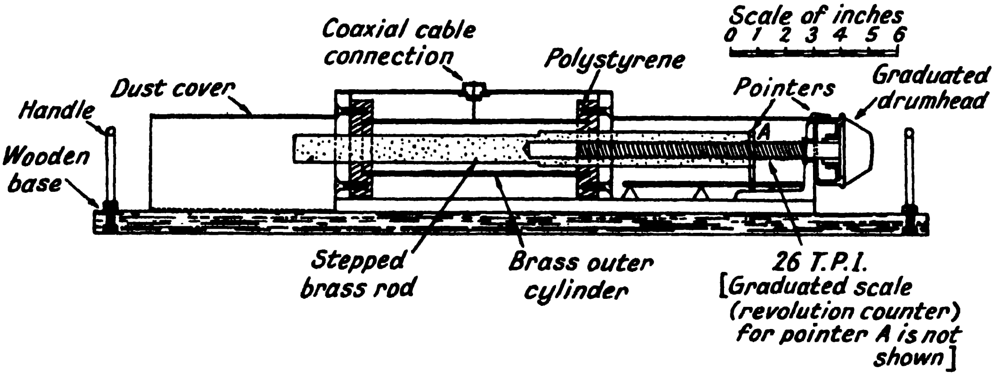
The cell-mounting, thermostat, and gas supply arrangements are substantially the same as those of I.G.R. above.

The Precision Condenser, C_p.—Details of this are shown as Fig. 4. It, as also that of I.G.R., utilises a "stepped-rod" on the principle described by Watson, Rao, and Ramaswamy (*Proc. Roy. Soc.*, 1934, **143**, 558), but with an altered design to provide a more rigid method of support of the high-potential component. Two polystyrene rings are grooved tightly to hold the brass cylinder, A (internal diameter 4·7 cm., length 20 cm.), and screwed to the ½" steel end-plates. Insulation by polystyrene is as efficient as the method used by Watson and obviously permits robust overall construction. The stepped brass rod (diameters, 3·0 and 2·68 cm.) is precision-turned to slide through two graphite-lubricated bearings (B) on the steel end-plates. The steel screw on which the stepped rod rotates has a pitch of 26 turns per in. and is ground true with the threaded sleeve of the rod. The total capacity of the condenser is *ca.* 30—40 pF. and the variable range 4 pF.

A moving pointer slides against a linear scale, indicating numbers of turns, while the rotating head (marked in hundredths) gives fractions of turns; readings are always taken in the same direction to avoid errors due to backlash. Each condenser shows satisfactory " straight-line " properties, confirmed by the fact that readings of capacity differences for a particular pressure of carbon dioxide at the same temperature are the same at any point on the scale. In practice most readings are taken over the middle of the scale because of possible end-effects.

FIG. 4.

Precision variable condenser.



Operation.—Routine procedure is as follows. The thermostat is set at the desired temperature and left for 12 hours during which the room reaches steady conditions (some radiation from the thermostat cannot be prevented). The oscillator etc. is then started and allowed to run for 5 hours at the frequency of the quartz. Meanwhile sulphur dioxide is collected in the apparatus. A series of readings at varying pressures (generally 12—16 pressures at a particular temperature, requiring some 2—3 hours) may now be taken. With the cell evacuated, the precision condenser is adjusted until zero current flows through the galvanometer. A second reading is obtained such that some 6—8 turns of the condenser are needed to pass from the first point on the current–capacity crevasse to that which is exactly opposite. This range provides the greatest sensitivity and stability. Next, the vapour is introduced into the cell, after 3 minutes the pressure is recorded, and capacity readings are taken as before. The cell is lastly evacuated, and after 3 minutes a final set of readings made. These timings are important if the mean of the two vacuum readings is to be the " true " vacuum reading corresponding to the vapour reading. This is so, since a slow drift in frequency cannot be entirely avoided. Providing, however, this is regular over 9 minutes (the period between two vacuum readings) it need not impair the measurements.

RESULTS.

The results are recorded as described by Le Fèvre and Russell (*loc. cit.*; see p. 378 for a sample set). The method used in a relative one, requiring preknowledge only of the polarisation of the standard gas (carbon dioxide in the present work). In what follows δC is the difference between drum and scale readings of the precision variable condenser when the cell is filled to a measured pressure, and the mean of the two " vacuum " readings taken before and after that particular " vapour " reading; p is the pressure in cm.

Values of $\delta C/p$ for each temperature are first plotted against pressure. A curved graph at this stage would suggest deviations from ideality of the gas, and/or to surface adsorption (Zahn, *Physical Rev.*, 1926, **27**, 329); however, in the case of carbon dioxide no such deviation occurs. We therefore take as the limiting value of $\delta C/p$ at zero pressure the arithmetic mean of the observed $\delta C/p$ readings.

Evidently the compressibility of carbon dioxide may be ignored. The measurement of pressure is actually used as an indirect measurement of the density of the gas, the underlying assumption being that δC (which is proportional to the change in dielectric constant) should be proportional to the number of molecules present per c.c., *i.e.*, to the density. For an ideal gas the density is proportional to the pressure, and $\delta C = k.p$. For a real gas we must substitute for p, the observed pressure, the " ideal pressure," p_i, that it would exert if Boyle's law were observed, *i.e.*, $\delta C = k.p_i = kp/(1 - Ap)$, where A is the compressibility; hence $\delta C/p = k/(1 - Ap)$.

This is a non-linear relation. Yet in the case of carbon dioxide, a linear graph, parallel to the p axis, is obtained. One can conclude therefore that for this substance compressibility considerations are unimportant. Direct experiments (Cawood and Patterson, *J.*, 1932, 2180; cf. Moles, Toral, and Escribano, *Trans. Faraday Soc.*, 1939, **35**, 1439) have shown very low A values, *e.g.*, 0·0053 at 21°, 0·0048 at 31° (where p is measured in *metres* of mercury). From these, even at room temperatures, the correction to $\delta C/p$ would amount only to $+\frac{1}{4}\%$ at 50 cm.

With sulphur dioxide below 100° the graphs *are* curved. They were accordingly extrapolated graphically to zero pressure, when, as may be seen from the equation above, $p = p_c$ and $\delta C/p = \delta C/p_c$. (For sulphur dioxide the compressibilities are 0·0165 at 30°, 0·0132 at 50°, corresponding in the first instance to a correction of +8% at 50 cm.) This extrapolation covers effects due to association of the molecules, which for sulphur dioxide is responsible for part of the compressibility. Gazulla and Perez (*Z. physikal. Chem.*, 1944, **193**, *A*, 162) find, from measurements of thermal conductivity, the equilibrium constant for the dissociation of the double molecule $(SO_2)_2$ to be given by $\log K_p = -8200/4{\cdot}573T + 8{\cdot}70$. At 40° and 1 atmosphere the partial pressure of $(SO_2)_2$ is thus only 1·14 cm., or 1·5% of the total pressure. This contribution tends, of course, to zero at $p \longrightarrow 0$.

Table I refers to carbon dioxide. To the "observed" figures in the third column the linear relation between $x' = (\delta C/p)_{p \rightarrow 0}$ and $1/T$ is fitted by the method of least squares. For the apparatus of I. G. R. we have $x' = 0{\cdot}3308 + 2083{\cdot}6/T$, while for that of B. M. S., $x' = 0{\cdot}0413 + 1408{\cdot}1/T$. The fourth column contains x' appropriately recalculated for each temperature. Also recorded are the pressure ranges, over which the readings were taken, and the number of observations made at each temperature.

TABLE I.

T (°K.).	Apparatus.	x'.	$x'_{\text{calc.}}$.	p range in cm.	No. of observations.
291·4	I. G. R.	7·47	7·48	15—69	9
317·8	,,	6·91	6·89	20—66	16
349·0	,,	6·38	6·30	20—93	13
375·1	,,	5·75	5·89	21—67	10
437·5	,,	5·14	5·10	21—66	18
289·3	B. M. S.	4·92	4·91	20—71	9
314·5	,,	4·51	4·52	23—73	12
351·2	,,	4·07	4·06	39—71	9
357·3	,,	3·99	3·98	22—76	14
373·0	,,	3·77	3·82	21—61	5
401·5	,,	3·60	3·55	39—70	10
429·0	,,	3·31	3·32	56—74	9
456·5	,,	3·13	3·14	37—75	10

TABLE II.

Polarisation of sulphur dioxide.

T(° K.).	Apparatus.	x.	P.	$P_{\text{calc.}}$.	$P_{\text{calc.}}$.	p range in cm.	No. of observations.
297·2	I. G. R.	65·2	65·99	65·86	65·30	13—66	15
340·1	,,	50·7	58·36	58·99	58·43	23—53	8
349·0	,,	4·86	57·32	57·76	57·22	20—65	10
351·0	,,	4·80	56·92	57·50	56·96	20—65	17
381·4	,,	4·19	53·74	53·82	53·29	20—67	11
408·5	,,	3·73	51·04	51·00	50·48	20—65	11
(437·0	,,	3·17	46·27	58·41	47·89	20—66	15)
296·2	B. M. S.	42·5	65·10	65·26	65·48	19—66	9
306·2	,,	40·0	63·22	63·48	63·70	19—69	11
307·3	,,	39·9	63·39	63·29	63·51	20—62	6
343·5	,,	32·9	58·27	57·75	57·96	30—63	7
382·5	,,	26·9	53·10	52·95	53·16	20—71	8
406·5	,,	24·0	50·27	50·46	50·67	21—65	13
440·5	,,	20·9	47·34	47·39	47·60	24—70	12
444·0	,,	20·6	47·02	47·10	47·31	24—71	18

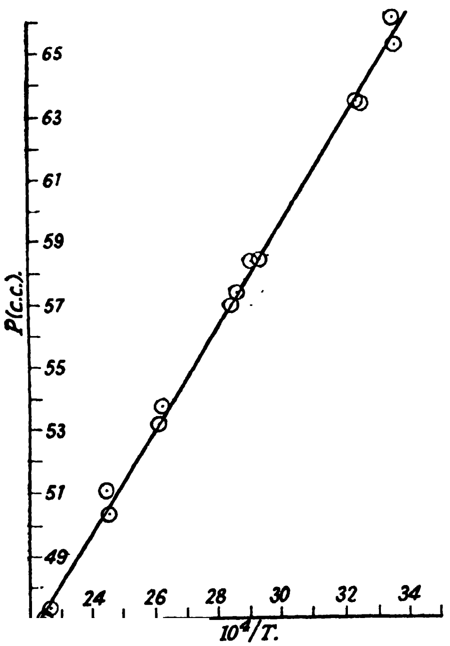
To evaluate the polarisation of sulphur dioxide, from parallel sets of measurements on this gas, we note that at zero pressure (where $\varepsilon + 2 = 3$) the Clausius–Mosotti expression becomes

$P = K(\delta C/p)_{p\to 0}(pv)_{p\to 0}$, where v is the volume occupied by one mole of gas. But in this limit $(pv)_{p\to 0} = p_c v_c$ (in the nomenclature above) $= v$, the molar volume of a perfect gas at one atmosphere. This is a general relation for all gases, K being a constant throughout. Therefore, if we put $(\delta C/p)_{p\to 0}$ for carbon dioxide $= x'$, and for sulphur dioxide $= x$, then $P_{SO_2} = P_{CO_2} \cdot x/x' = 7{\cdot}341\ x/x'$ c.c. (using the polarisation of carbon dioxide given at the beginning of this paper).

The values thus determined for P_{SO_2} are plotted against $1/T$, and straight lines again fitted by the method of least squares. The results are shown in Table II.

Fig. 5 shows the observed polarisations (column 4 of Table II) superimposed on the graph of $P = 10{\cdot}91 + 16164/T$ (column 6 of Table II). Column 5 of Table II gives the polarisations calculated from each set of data separately by the equations: $P = 11{\cdot}31 + 16213/T$ (I. G. R.) and $P = 10{\cdot}72 + 16155/T$ (B. M. S.). The incomplete agreement seems to be connected more with the shape and layout of components than with the manner in which the apparatus is operated. Relative performance may be examined by the scatter of $\delta C/p$ for a particular gas at a given temperature. In the above determinations the estimated order of accuracy is about ±1% for carbon dioxide. For sulphur dioxide, with $\delta C/p$ about nine times as great, the corresponding figure is *ca.* ±0·2%, not ±0·1% as might be expected. The loss of accuracy is due probably to slight imperfections in the precision condensers, which necessarily have a very slight longitudinal play (to enable screw action to take place at all), quite apart from any deviations from linearity in capacitance, and to actual mechanical changes occasioned by rotating their drumheads upwards of 50 times between vacuum and gas readings.

FIG. 5.



The expressions just written for P should be compared with $10{\cdot}64 + 16100/T$, computed by us from data recorded by Zahn (*Physical Rev.*, 1926, **27**, 455). Earlier papers by Badeker, Klemenčic, and Verain (references and summaries in "International Critical Tables," Vol. VI, p. 74) give dielectric-constant estimations at too few set temperatures and pressures to permite valuation of the constants A and B in the Debye equation. Jona (*Physikal Z.*, 1919, **20**, 14), however, reports fuller figures; from these we calculate [using $(\varepsilon - 1)/(\varepsilon + 2)$, and least squares]: $P = 20218/T - 0{\cdot}194$. A negative A term is, of course, impossible and must be attributed to experimental errors, which A reflects sensitively.

The Dipole Moment of Sulphur Dioxide.—This, from $\mu = 0{\cdot}01273B^{\frac{1}{2}}$, is, for the various B values already given, 1·619 D. ($B = 16164$), 1·620 D. ($B = 16213$), 1·618 D. ($B = 16155$), and 1·615 D. ($B = 16100$; Zahn), 1·81 D. ($B = 20218$; Jona).

The Faraday Society Table of dipole moments (Appendix to *Trans.*, 1934, **30**) shows, under sulphur dioxide, a reference to Braunmühl, whose paper does not however include this substance. It further quoted Jona's result as $\mu = 1{\cdot}76$ D., but this appears to have been obtained using $P = V(\varepsilon - 1)/3$. We have given special consideration to the experiments of Jona, since, in contrast with the estimates (1·615—1·619) by Zahn and us, his datum resembles the higher group (1·7—1·9 D.) drawn from observations of electrostriction (Frivold, *Physikal. Z.*, 1921, **22**, 603; Kliefoth, *Z. Physik*, 1926, **39**, 402). This phenomenon, however, does not yet rest upon a proven theoretical basis, and the measurements involved (changes in volume of *ca.* 3×10^{-4} c.c.) are very delicate. Frivold, in three determinations between 292·0° and 292·8°, found $\mu = 1{\cdot}74$, 1·90, and 1·86 D. High field strengths, E, being employed, Kliefoth questioned the sufficiency of the simple (Gans) relation, used by Frivold, namely: $\delta v/v_0 = E^2(\varepsilon - 1)/8\pi p$, and considered the effect of higher powers of E. It is significant that his estimate for μ_{SO_2} is 1·7 D.—*i.e.*, lower than Frivold's.

Jona was among the first to use a heterodyne-beat H.F. method but during the 30 years since his publication there has been great improvement in radio components and practice. His figure, moreover, may be offset by lower ones, calculable by the refractivity method from the single ($\varepsilon - 1$) measurements of other earlier workers : 1·61 D. from Klemenčic (*Sitzungsber. Akad. Wiss. Wien*, 1885, II, **91**, 712) ; 1·60 D. from Bädeker (*Z. physikal. Chem.*, 1901, **36**, 305) ; 1·59 D. from Verain (*Ann. Physique*, 1914, **1**, 255).

For the above reasons, and noting the near agreement between Zahn and ourselves, we record the dipole moment of sulphur dioxide as 1·619 D.

Atomic Polarisation of Sulphur Dioxide.—The refractive index of this gas has been measured by, *inter alia*, Cuthbertson and Cuthbertson (*Proc. Roy. Soc.*, 1909, *A*, **83**, 171) and Huxley and Lowery (*ibid.*, 1943, *A*, **182**, 207). The last-named authors have reviewed the subject and reported an extended study of the dispersion. From their Sellmeier formula : $(n - 1)_0 = 5{\cdot}220 \times 10^{27}/(8178 \times 10^{27} - \nu^2)$ we estimate n^2_∞ to be 1·001277, and (V_0 being 22·4141, *vide* International Critical Tables, Vol. 3, p. 3) R_∞ to be 9·54 c.c. A corresponding computation from the Cuthbertson data yields 9·58 c.c. These are close to the $[R_L]_D$ of 9·49 c.c. found by Nasini (*Gazzetta*, 1883, **13**, 296). The A value (cf. p. 282) cannot be more certain than 10·9 ± 0·6, so that ${}_AP = 1{\cdot}4 \pm 0{\cdot}6$ c.c., *i.e.*, from 1 to 3% of the total polarisation at room temperatures or 8—21% of ${}_EP$ (for comparison, the analogous % for carbon dioxide is 12 ; Watson and Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144). We have attempted its *a priori* calculation, following Coop and Sutton (*J.*, 1938, 1280). Wagner (*Z. physikal. Chem.*, 1943, *A*, **193**, 55), from Raman spectra, gives the O–S–O angle as 135° and the O–O force constant as $1{\cdot}217 \times 10^5$ dynes/cm. If $r_{S\text{–}O} = 1{\cdot}43 \times 10^{-8}$ cm. (Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1940, **62**, 1270), $f_{\text{bending}} = V_0 = 2{\cdot}49 \times 10^{-11}$ ergs/radian ; or, with $r_{S\text{–}O} = 1{\cdot}37 \times 10^{-8}$ cm. (Sponer, " Molekülspektren," Springer, 1935), $V_0 = 2{\cdot}28 \times 10^{-11}$ ergs/radian (we note that the corresponding figure for ozone is $2{\cdot}34 \times 10^{-11}$, *i.e.*, of the same order ; Simpson, *Trans. Faraday Soc.*, 1945, **41**, 215). For the apical angle quoted, $\mu_{S\text{-}O}$ is 2·12 D. ; for one of *ca.* 120° (as earlier reported by Dadieu and Kohlrausch, *Physikal. Z.*, 1932, **33**, 165) it is 1·62 D. Coop and Sutton (*loc. cit.* ; cf. Bloom and Sutton, *J.*, 1941, 727) give ${}_AP = 4\pi nN\mu_1^2/9V_0$, where n is the number of angular co-ordinates necessary to express completely the possible independent modes of bending of the opposing dipoles, each of magnitude μ_1. Sutton's actual cases (*e.g.*, *p*-benzoquinone) all had high degrees of symmetry. Dekker (*Rec. Trav. chim.*, 1945, **64**, 126) has applied Sutton's equation to triangular molecules by using $\mu_1 \sin (\alpha/2)$ instead of μ_1 (2α = angle between valency bonds). For sulphur dioxide he estimates ${}_AP$ as 0·07 c.c. This seems unnecessarily small, for from the figures given above we find the lowest ${}_AP$ to be 0·13 c.c., and the highest 0·28 c.c. Nevertheless, the observed quantity is much larger. The computation is sensitive to 2α. Thus, using the lower $r_{S\text{-}O}$ and V_O values, for 2α = 120°, 135°, 140°, 150°, 155°, and 160°, atomic polarisations follow of respectively 0·15, 0·28, 0·37, 0·68, 1·00, and 1·56 c.c.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, September 12th*, 1949.]

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60. *Sulphur Dioxide. Its Apparent Dipole Moment as a Solute and as a Pure Liquid compared with the True Value as a Gas.*

By R. J. W. LE FÈVRE and I. G. ROSS.

Measurements at 25°, and calculations by the Debye–Clausius–Mosotti formulæ, provide moments of $1{\cdot}6_1$ D. (in benzene), $1{\cdot}6_2$ D. (in carbon tetrachloride), *ca.* 1·4 D. (in chloroform), and $1{\cdot}1_6$ D. (as pure liquid).

Sulphur dioxide is the simplest molecule with a negative Kerr constant whose apparent dipole moments as liquid, or in solution, have been compared with the true value (*i.e.*, $1{\cdot}6_2$ D., see preceding paper) as measured in the gaseous state.

The ratios found for $\mu_{\text{liq.}} : \mu_{\text{gas}}$ or $\mu_{\text{soln.}} : \mu_{\text{gas}}$ disagree with forecasts based on various previous formulæ or " rules " for the effects of media on μ_{apparent}. Theories utilising the conception of hindered molecular rotation in liquid systems are also unsatisfactory in their present forms. A recent treatment of the $\mu_{\text{soln.}} : \mu_{\text{gas}}$ aspect of the problem by Ross and Sack, however requires a small *diminution* in μ_{apparent} on dissolution in benzene or carbon tetrachloride. The experimental indications are that the direction of change is as predicted.

FOR the purpose indicated in paragraph (*a*) of the opening of the previous paper, we required dielectric polarisation data for sulphur dioxide, both as a pure liquid, and as a solute in a non-polar solvent. The literature, however, contained only a few ε and d points for the former state, and none for the latter. We have therefore made appropriate measurements on sulphur dioxide–benzene and sulphur dioxide–carbon tetrachloride systems. These are now recorded, together with the details of our redetermination of ε_{SO_2}.

Solutions of Sulphur Dioxide.—These were made up by dissolving the gas in a weighed amount of solvent and observing the increase of weight.

For benzene, in which sulphur dioxide is extremely soluble, the solution was prepared by attaching the flask to the outlet tube *C* of the gas apparatus (see Fig. 3, preceding paper), and controlling the vaporisation of purified liquid sulphur dioxide so as to maintain a gas pressure of about 1½ atmospheres. The flask was cooled to *ca.* 5° and shaken occasionally, absorption taking place readily, about 2 hours sufficing to make up a solution of adequate concentration. By not passing the gas *through* the liquids the possibility of solvent loss (which would result in an underestimate of the weight fraction) was avoided.

For carbon tetrachloride, with which this process would have been tedious, owing to the lower solubility, a small quantity of liquid sulphur dioxide was collected in a test tube attached to the ground glass cone on *C*. When the gas pressure had reached atmospheric, the tube was detached and the contents introduced into the weighed benzene, the flask being closed with a rubber stopper, and reweighed.

The *density* measurements were made with a Sprengel pyknometer of about 10 ml. capacity, with capillary side-arms. The liquid was moved by pressure of dry air, rather than by suction, which caused liberation of gas. Even so, evolution of vapour did occur at times during adjustment in the thermostat, and the accuracy of the measurements, while adequate, is less than that made with non-volatile solutes. The *dielectric constant* determinations were made with the resonance apparatus described by Calderbank and Le Fèvre (*J.*, 1948, 1949). The cell was filled and emptied by air pressure. The results are given in Table I, the symbols being those customarily used by us (cf. *J.*, 1937, 1805).

TABLE I.

Sulphur dioxide in benzene.						Sulphur dioxide in carbon tetrachloride.		
10^6w_1.	$(d_{12})^{25}_4$.	$(\varepsilon_{12})^{25}$.	β.	$\alpha\varepsilon_2$.	${}_TP_1$.*	10^6w_1.	$(\varepsilon_{12})^{25}$.	$\alpha\varepsilon_2$.
0	0·87378	2·2725	—	—	—	0	2·2261	—
14396	0·87821	2·3508	0·351	—	—	7438	2·2805	7·32
29537	0·88179	2·3853	0·354	4·35	58·8	7834	2·2835	7·29
34459	0·88462	2·4241	0·360	4·40	64·6	8972	2·2884	6·95
40972	0·88690	2·4515	0·366	4·37	63·8	12178	2·3127	7·11
59644	0·89252	2·5409	0·360	4·50	64·1	24634	2·3994	7·04
73010	0·89705	2·6117	0·364	4·61	64·6	31909	2·4354	6·56

* Calculated by Sugden's equation (*Trans. Faraday Soc.*, 1934, **30**, 720).

From the above data for benzene as solvent the dipole moment can be evaluated: mean $\beta = 0{\cdot}359_2$, $\alpha\varepsilon_2 = 4{\cdot}21 + 5{\cdot}20w_1$ whence ${}_TP_\infty = 64{\cdot}72$ c.c., and—since the distortion polarisation $= 10{\cdot}9_1$ c.c. (cf. preceding paper)—$\mu = 1{\cdot}61_2$.

With carbon tetrachloride as solvent, our density determinations produced somewhat scattered values ($-0{\cdot}21$ to $-0{\cdot}32$) for β. Recourse was therefore made, as a check, to the careful dilatometric measurements of Horiuchi (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1931, **17**, 126) on solutions of gases in certain organic liquids. Extrapolation to zero concentration of Horiuchi's figures for the coefficient of dilatation, δ, of sulphur dioxide in carbon tetrachloride gives $\delta = 2{\cdot}435 \times 10^{-3}$. If the density of sulphur dioxide at N.T.P. is taken as 2·9269 g./l. (International Critical Tables, Vol. **3**, p. 3), the limiting rate of decrease in density with concentration of sulphur dioxide can be calculated; whence $\beta = -0{\cdot}318$. (A similar calculation with benzene, taking $\delta = 2{\cdot}138 \times 10^{-3}$, gave $\beta = +0{\cdot}363$, in good agreement with our direct measurements in this medium.) We note that the densities of the two weakest sulphur dioxide–carbon tetrachloride solutions (11—16%) used by Adams and Rogers (*J. Amer. Chem. Soc.*, 1939, **61**, 112) correspond to a β of $-0{\cdot}22$. Nevertheless, since both $1 - \beta$ and $\alpha\varepsilon_2$ increase with dilution, we have taken $-0{\cdot}318$ and 7·32 respectively (whence ${}_TP_\infty = 65{\cdot}15$ c.c. and $\mu = 1{\cdot}61_8$ D.) to provide a maximum estimate of the apparent moment.

Six solutions of sulphur dioxide in chloroform were also examined but were marred by unavoidable escapes of gas. The approximate values obtained for β and $\alpha\varepsilon_2$ were $-0{\cdot}11$ ($\pm0{\cdot}01$) and 8·4 ($\pm0{\cdot}25$) respectively; from these, μ is *ca.* 1·4 D.

Liquid Sulphur Dioxide.—A number of measurements of the dielectric constant of this material are on record. Coolidge (*Wied. Annalen*, 1899, **69**, 125), using Drude's second method (*ibid.*, 1897, **61**, 466), found $\varepsilon = 13{\cdot}75$ at 14—15° (frequency 300 mc./s.). Schlundt (*J. Physical Chem.*, 1901, **5**, 157, 403), with the same method, gave $\varepsilon = 12{\cdot}35$ at 22°, while Verain (*Ann. Physique*, 1914, **1**, 523) obtained values about half those reported by previous workers. Everscheim (*Ann. Physik*, 1902, **8**, 539) used a bridge method, and covered the temperature range from 114° to 157·5°, just above the critical temperature. His results can be summarised (when $0° < t° < 150°$) by the relation: $\varepsilon_{t°} = 15{\cdot}6 - 0{\cdot}078t$. Using Everscheim's temperature coefficient of ε, we may reduce these readings to a single temperature (0°) for comparison: 14·9 (Coolidge), 15·5 (Schlundt), 14·6 (Everscheim).

Coolidge and Schlundt, and presumably also Everscheim (although this is not explicit in his paper), used for calibration various benzene–acetone mixtures, whose dielectric constants had been measured by Drude (*loc. cit.*). In our experience pure acetone is a most difficulty reproducible substance for use as a standard, and, in this connection, we would emphasise that the value quoted by Drude for $\varepsilon_{\text{benzene}}$ at 19° (2·260) is markedly less than the value (2·2846) given by Hartshorn and Oliver (*Proc. Roy. Soc.*, 1929, *A*, **123**, 666).

Having found that the overall capacity of his cell, empty, did not vary measurably with temperature (a likely result if the effect of changes in cell dimensions due to expansion of the condenser and glass container are analysed), Everscheim used throughout the whole temperature range the value of the replaceable cell capacitance as measured at one temperature. His measurements are therefore probably all in error by a constant factor, depending on the calibration of his cell and the purity of his material.

We have accordingly re-measured the dielectric constant of sulphur dioxide at 0° (when the vapour pressure is only 1·53 atm.) and used the (corrected) slope of Everscheim's graph to calculate the value of 25° (vapour pressure, 3·82 atm.). By working at the lower temperature, the system could be closed with ordinary taps, instead of sealing off the inlet tubes, thus considerably lessening the chance of disturbing the cell and leads between readings.

To this end, a cell was used, consisting of two coaxial brass tubes, $\frac{1}{2}''$ and $\frac{5}{8}''$ external diameter, and 13 mm. (inner) and 15 mm. long respectively, spaced by four glass beads (diameter *ca.* 1 mm.), fitting into shallow sockets on the inner cylinder. The assembly hung rigidly from two stout tungsten wires which passed through the glass (" Pyrex ") into mercury-filled cups, whence leads were taken to a coaxial cable connector, fixed on the wooden bridge locating the cell in a constant temperature bath. The latter was a lagged 3-l. beaker, filled with ice and water and provided with a levelling device. Adequate stirring, it was found, could be achieved by dropping a few small fragments of solid carbon dioxide into the bath.

The capacitance measurements were performed with an apparatus similar to that used for measuring the dielectric constants of sulphur dioxide solutions.

The cell was calibrated at 0°, using five liquids whose dielectric constants had been determined at this temperature by Le Fèvre (*Trans. Faraday Soc.*, 1938, **34**, 1127), together with ethylene dichloride.

It was found that for any given liquid, the value of $(C_{\text{liq.}} - C_{\text{air}})$ was reproducible to better than two scale divisions of the variable condenser connected in parallel with the cell, a liquid with $\varepsilon - 1 = 2$ giving a difference of approx. 200 such divisions.

The results of this calibration are given in Table II, the cell constant being the replaceable capacitance, measured in divisions of the condenser scale.

Table II.

Calibration of liquid cell.

Liquid.	$(C_{\text{liq.}} - C_{\text{air}})$.	$\varepsilon - 1$.	Cell constant.
Carbon tetrachloride	131	1·2734	102·9
Toluene	144	1·4350	100·3
Ether	379	3·803	99·7
Chloroform	433	4·189	103·5
Ethyl bromide	933·5	9·19	102·0
Ethylene dichloride	1038·5	10·514	103·5

Acetone ($\varepsilon - 1 = 20·58$) was also used, but with it the resonance curve was damped and widened. Rejecting the ether reading as improbably low, and noticing that any error in the cell constant calculated from toluene is magnified by the fact of its having a small dielectric constant, we adopted the mean value of 103 for the cell constant, with a probable error of about ±1%. We are not justified in assuming any deviation from linearity of $(C_{\text{liq.}} - C_{\text{air}})$ with dielectric constant.

The value taken for the dielectric constant of ethylene dichloride needs further comment, in view of the recently published value (extrapolated to 0°) of 11·77 (Clay, Dekker, and Hemelryk, *Physica*, 1943, **10**, 768). The figure used in Table II is that found by Davies (*Phil. Mag.*, 1936, [vii], **21**, 1008), whose objective was to establish this liquid as a standard substance. Davies has reviewed determinations prior to his own; most of those which are subsequent, despite their claimed accuracy of 0·02%, are not supported by details of any practical re-examination of the problem of obtaining reproducibly purified specimens. The earlier figure, due to Davies, has accordingly been retained.

Sulphur dioxide, from a cylinder, was dried by repeated fractional distillation over phosphoric oxide, the gas being passed each time through phosphoric oxide–glass wool bulbs. It was finally distilled from fresh phosphoric oxide directly into the cell, which for the purpose was connected *via* its right-hand arm to the outlet tube *C* of the gas-handling apparatus (Fig. 3, preceding paper) by thick-walled rubber tubing, the system being made vacuum tight. When surrounded by alcohol at about −80°, the cell took 1—2 hours to fill. This accomplished, the alcohol was replaced by ice-water, and the capacitance measured when stationary conditions had been attained. The sulphur dioxide was then cautiously allowed to boil off, air (dried by passage over 5 feet of P_2O_5) passed through for about a minute, and the " air " reading taken. The differences, $C_{\text{liq.}} - C_{\text{air}}$, so obtained were constant at 1450·0, whence $\varepsilon_{SO_2} = 15·0_8$ at 0°, and (using the corrected $\delta\varepsilon/\delta t$ of $-0·075$) 13·20 at 25°.

From these quantities the " apparent " dipole moments according to the formulæ of Debye, ${}_{O}P = M[(\varepsilon - 1)/(\varepsilon + 2) - (n^2 - 1)/(n^2 + 2)]/d$, and Onsager, ${}_{O}P = M(\varepsilon - n^2)(2\varepsilon + n^2)/d\varepsilon(n^2 + 2)^2$, can now be calculated approximately. The refractive index, *n*, of sulphur dioxide for the D line at 20° is 1·342 (Nasini, *Gazzetta*, 1883, **18**, 296) corresponding approximately to 1·362 at 0° (Bleekrode, *Proc. Roy. Soc.*, 1884, **37**, *A*, 339). Nasini (*loc. cit.*), Cailletet and Matthias (*Compt. rend.*, 1887, **104**, 1564), Lange (*Z. angew. Chem.*, 1899, **12**, 277), Stowe (*J. Amer. Chem. Soc.*, 1929, **51**, 410), Seyer and Peck (*ibid.*, 1930, **52**, 14), and Eversole, Wagner, and Bailey (*J. Physical Chem.*, 1941, **45**, 1388), quote densities for liquid sulphur dioxide which, after conversion to 0° and 25°, provide the average values 1·435 (0°) and 1·369 (25°).

By substitution, we find:

		0°.	25°.
Debye equation	$_0P$	27·0 c.c.	27·3 c.c.
	μ	1·10 D.	1·16 D.
Onsager equation	$_0P$	84·4 c.c.	79·4 c.c.
	μ	1·93 D.	1·96 D.

For large values of ε, the Debye expression is highly insensitive to small variations in this quantity. With regard to the Onsager equation, it can easily be shown that for ε *ca.* 15, n^2 *ca.* 2, $\Delta_0P/_0P = -0{\cdot}87\ (\Delta n^2/n^2) = 1{\cdot}34\ (\Delta\varepsilon/\varepsilon) = -\Delta d/d$, and that it will therefore be affected chiefly by errors in ε. These we estimate generously at $\pm 1\%$, whence the uncertainty in $_0P$ is $\pm 1{\cdot}2$ c.c., and in μ, $\pm 0{\cdot}07$ D.

Discussion.—As a preliminary, the foregoing experimental results (as calculated by the Debye equation) are summarised in convenient form as Table III.

TABLE III.

State.	Gas.	Solution in C_6H_6.	Solution in CCl_4.	Solution in $CHCl_3$.	Liquid.
$_TP_{\text{apparent}}$	65·15	$64{\cdot}7_2$	$65{\cdot}1_5$ †	51·2	38·2
$\mu^2_{\text{apparent}}/\mu^2_{\text{gas}}$	—	$0{\cdot}99_2$	1·00 †	0·74	0·50
$\delta\mu^*/\mu_{\text{gas}}$	—	$-0{\cdot}00_4$	0 †	−0·136	−0·28

* $\delta\mu = \mu_{\text{liquid}}$ or $\mu_{\text{soln.}}$ minus μ_{gas}. † A *maximum* estimate, cf. p. 284.

Solutions of Sulphur Dioxide.—The particular relevance of sulphur dioxide as a substance for the investigation of solvent effects lies in the fact that it is a relatively simple molecule of shape not greatly different from ellipsoidal, and possessing a negative Kerr constant (K at 760 mm. for light of 5400 A. $= -9{\cdot}4 \times 10^{-15}$; Stuart and Volkmann, *Ann. Physik.*, 1933, **18**, 140). It is thus well suited for testing the rule—first devised by Goss (*Trans. Faraday Soc.*, 1934, **30**, 751) on the basis of the Raman–Krishnan theory (*Proc. Roy. Soc.*, 1928, *A*, **117**, 589) of the dielectric constant of anisotropic liquids (as applied to liquid mixtures) and subsequently advanced by Higasi (*Sci. Papers Inst. Phys. Chem. Res. Toyko*, 1936, **28**, 284) from a different viewpoint—that the sign of the solvent effect should be opposite to that of the Kerr constant of the substance. This rule was dependent upon the consideration of spheroidal molecules, or of those which could be regarded as approximately spheroids; recently, however, Ross and Sack (*Proc. Physical Soc.*, in the press), by widening the Raman–Krishnan and Higasi arguments to ellipsoidal molecules with *three unequal* axes, have shown that even on the basis of these—themselves not complete treatments—the Kerr constant rule could not have had a completely general applicability; indeed for molecules in which the resultant moment is parallel to the mid-axis of its ellipsoidal approximation—and sulphur dioxide is one such—the sign and magnitude of the Kerr constant need give no indication at all of the sign and magnitude of the solvent effect.

By extending Onsager's approach (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) to the static dielectric constant of liquids and solutions (again, the original was derived for spherical molecules only) to ellipsoidal molecules of uniform polarisability, Ross and Sack obtain a new expression for the solvent effect, in which the sign of $\delta\mu$ depends not only on the shape of the solute molecule but also on its refractive index and on the dielectric constant of the solvent medium. We merely note here, quoting from their paper, and applying their calculation also to the carbon tetrachloride solution, that while the generalised Higasi theory, even in an amended form [which tends to reduce $\delta\mu/\mu$ by a factor of $(\varepsilon + 2)/3\varepsilon$], requires a $\delta\mu/\mu = +0{\cdot}011$ in both benzene and carbon tetrachloride, the Ross–Sack equation leads to $\delta\mu/\mu = -0{\cdot}016$ (in benzene) and $-0{\cdot}012$ (in carbon tetrachloride). Thus, while it is not correct quantitatively, the new equation is qualitatively so in successfully covering the small decrease in apparent moment, noted (cf. Table III) with the former solvent, and inferred for the latter.

We conclude therefore, from both the theoretical considerations of Ross and Sack and the experimental evidence presented here for sulphur dioxide, that values of the Kerr constant can no longer be regarded as a satisfactory basis for predictions concerning the solvent effect.

Liquid Sulphur Dioxide.—It is now generally recognised that the assumptions made in the derivation of the Debye equation are too drastic to allow it to be used to calculate the dipole moments of molecules from measurements of the pure liquid substances; the data in the last column of Table III concerning liquid sulphur dioxide illustrate this.

Onsager's expression (cf. p. 285) for spherical isotropic molecules has been found to be of more general applicability. It has been critically tested on 31 pure liquids by Böttcher

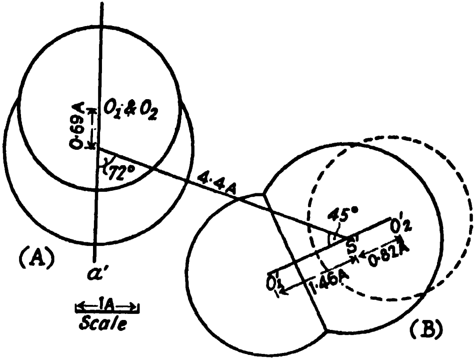
(*Physica*, 1939, **6**, 59), who finds it to give values of μ_{apparent} in good accord with μ_{gas}. Wilson (*Chem. Reviews*, 1939, **25**, 377), however, has pointed out that in view of Onsager's neglect of association effects and of molecular anisotropy, this agreement is probably fortuitous. He also suggests that instead of using for n the extrapolated value of the refractive index at infinite wave-length, the effective refractive index, defined by: $(n^2_{\text{eff.}} - 1)/(n^2_{\text{eff.}} + 2) = 4\pi N\alpha/3 = d({}_{\text{E}}P + {}_{\text{A}}P)/M$ should be taken, where $({}_{\text{E}}P + {}_{\text{A}}P)$ is the observed distortion polarisation (preferably from gas measurements).

Wilson has adapted Onsager's theory to cover the anisotropy of the molecular units forming a liquid: if n_2 is the effective refractive index corresponding to the polarisability α_2 along the dipole axis (defined by an equation similar to that just written), and if n is the average effective refractive index, then $M(\varepsilon - n^2)/d\varepsilon(2\varepsilon + n^2) = 4\pi N\mu^2 (n_2^2 + 2)^2/9kT(2\varepsilon + n_2^2)^2$ and n_2 can be estimated from Kerr constant–polarisability data. The results of these several calculations applied to sulphur dioxide at 25° are as follows:

Data used: ${}_{\text{E}}P + {}_{\text{A}}P = 10{\cdot}9$; $d = 1{\cdot}369$, $\varepsilon = 13{\cdot}20$, $n^2_{\text{eff.}} = 1{\cdot}911$, $n_2^2 = 1{\cdot}769$.
Onsager's equation (using $n^2_{\text{eff.}}$): ${}_{\text{O}}P_{\text{liq.}} = 74{\cdot}07$. ${}_{\text{O}}P_{\text{liq.}}/{}_{\text{O}}P_{\text{gas}} = 1{\cdot}365$.
Wilson's equation: ${}_{\text{O}}P_{\text{liq.}} = 78{\cdot}31$, ${}_{\text{O}}P_{\text{liq.}}/{}_{\text{O}}P_{\text{gas}} = 1{\cdot}444$.
Kirkwood's equation (see below); $g = 1{\cdot}399$.

It will be observed that Onsager's equation (even when $n^2_{\text{eff.}}$ is used in place of n^2), as well as Wilson's extension of it, lead to predicted values of the orientation polarisation approximately 40% too high.

An explanation of the increased apparent moment of sulphur dioxide in the liquid state, as indicated by these equations, may be found in the results of an *X*-ray examination of liquid sulphur dioxide at room temperature by Bastiansen and Finbak (*Tids. Kjemi Bergwesen Met.*, 1945, **4**, 2). Their figures for the shape of the sulphur dioxide molecule in the condensed phase agree exactly with the figures of Pauling and Brockway (*J. Amer. Chem. Soc.*, 1935, **57**, 2684) for the gas. They give also intermolecular distances and angles which describe a quasi-crystalline structure with 4-fold (tetrahedral) co-ordination of sulphur dioxide molecules about a central molecule. Unfortunately, these authors do not show the relative disposition of any two complete adjacent molecules, but we may determine this by applying the reasonable principle that, of the four molecules *B*, *C*, *D*, and *E*, surrounding a central molecule *A*, two, say *B* and *C*, must be disposed with respect to *A*, as is *A* with respect to *D* and *E*, since *A* is one of the four molecules adjacent to each of the latter. Then it is found that on the figures of Bastiansen and Finbak only one type of mutual orientation is possible. This is shown in the figure; the dotted O atom is the one whose position we infer; it lies either above or below the plane of the figure; the two O atoms of the central sulphur dioxide molecule *A* lie in the plane through *aa'* perpendicular to the plane of the figure. A second molecule *B* can occupy the positions similar to those of *B* on the other side of *aa'*, and *D* and *E*, the locations of whose S atoms only are given by Bastiansen and Finbak, are in front of and behind, respectively, and above, *A*, disposed in the same way as *A* is to *B*. If we calculate the field due to each of the four dipolar molecules at *A* (assuming the intervening dielectric to be uniform, *i.e.*, no refraction of the lines of force) it is found that in each case there is a component parallel to and in the same sense as the dipole of *A*; the components perpendicular to this will cancel on the average, in view of the choice of positions available for each of *B*, *C*, *D*, *E*. Thus there is a polarising field producing an additional moment which, combined vectorially with the original moment, must increase it; to attempt to calculate precisely this short-range dipolar action would involve too many assumptions, but the general conclusion, that it will reinforce rather than detract from the original moment, still holds.



Finally, Onsager's equation has been further modified by Kirkwood (*J. Chem. Physics*, 1939, **7**, 911; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 315), who has allowed, in principle, for a mutual action of any kind between the molecules, although—since this action cannot yet be evaluated in precise terms—the equation he derives is not amenable to direct test. Kirkwood finds $M(\varepsilon - 1)(2\varepsilon + 1)/9\varepsilon d = {}_{\text{E}}P + {}_{\text{A}}P + 4\pi N\mu\bar{\mu}/9kT = {}_{\text{E}}P + {}_{\text{A}}P + 4\pi N\mu^2 g/9kT$. Here μ is the dipole moment of the molecule in the absence of an applied field, and is evaluated sufficiently accurately by the relation due to Onsager (*loc. cit.*) : $\bar{\mu} = \frac{2\varepsilon + 1}{2\varepsilon + n^2} \cdot \frac{n^2 + 2}{3} \cdot \mu_0$; $\bar{\mu}$ is the total moment of a molecule and its neighbours in the region surrounding it, in which the local dielectric constant differs effectively from the overall macroscopic value.

The " correlation parameter," g, is a measure of the degree and strength of association of the molecules in the liquid. For water and alcohols, which have strong intermolecular hydrogen bonding, Oster and Kirwood (*J. Chem. Physics*, 1943, **11**, 175) have attempted to evaluate g theoretically (but even then on questionable assumptions; Frenkel, " Kinetic Theory of Liquids," Oxford, 1946). For sulphur dioxide, which has no such strong bonding, this is not possible.

However, g is accessible from experimental data, and the value obtained (see above) shows that sulphur dioxide falls in the same class as liquids such as ammonia, ether, acetone, and nitrobenzene, for all of which g is in the range 1·1 to 1·7; we conclude therefore that sulphur dioxide shows especially marked association.

In this connection we would mention that the extraordinary mutual solubility of benzene and sulphur dioxide (amounting to complete miscibilty of two substances which are chemically dissimilar) might lead to a suspicion that some sort of association of a more formal kind than the type so far considered may exist in these mixtures, although the freezing-point curve gives no indication of this. Seyer and Peck (*J. Amer. Chem. Soc.*, 1930, **52**, 14), from determinations of the Eötvös constant, inferred that sulphur dioxide was associated only below 0°, and not noticeably so in mixtures. In harmony with this, we find the total polarisations (cf. Table I, p. 284) to be substantially independent of concentration. There seems, therefore, to be no evidence for the formation of sulphur dioxide–benzene complexes. Viscosity data (Adams and Rogers, *J. Amer. Chem. Soc.*, 1930, **61**, 112) suggest a similar conclusion for the system sulphur dioxide–carbon tetrachloride.

Concerning the pure liquid, in addition to the remarks of Seyer and Peck, we note that Awbery and Griffiths (*Proc. Physical Soc.*, 1936, **48**, 372) report sulphur dioxide as obeying Herzog and Kudar's relation (*Z. Physik*, 1933, **80**, 217) between latent heat of fusion and viscosity, *i.e.*, behaving as an unassociated liquid.,

The foregoing review offers nothing to support the discussion of Le Fèvre and Le Fèvre (*J.*, 1935, 1747; 1936, 487) or that of Le Fèvre and Russell (*J.*, 1936, 491), both of which assumed solute association in pairs at least. Statements made in the second 1936 paper require amendment in the light of the measurements now recorded for sulphur dioxide. Thus the sign of the Kerr constant was introduced through a structural coincidence, molecules for which K is positive or negative being classed as " type A " or " type B " respectively. Further, both these " types " were idealised (cf. diagrams on p. 1784 of the 1935 ref.) beyond usefulness where sulphur dioxide is concerned, since the mutual orientation of the sulphur dioxide molecules in the liquid, as indicated by X-ray evidence and supported by apparent moment determinations, corresponds in no way to the type of association postulated for molecules of type B, which, it was put forward, should pack together collinearly, with their dipoles parallel and in line. In particular, the predictions made by Le Fèvre and Russell (second 1936 ref. above) for cases where a solute and solvent are each of B type, are shown to be incorrect by the present findings for sulphur dioxide in chloroform and in itself.

Theories Involving Hindered Rotation in Liquids.—A number of other attempts have been made to introduce features of the structure of liquids into discussions of their dielectric properties. Stewart's idea of cybotaxis (*Rev. Mod. Physics*, 1930, **2**, 116; *Physical Rev.*, 1931, ii, **37**, 9), and the experimental evidence behind it, seem particularly suggestive, in that the predisposition of a liquid to contain more or less ordered arrangements over small elements of its volume springs from the anisotropic properties of the molecules concerned. Debye (*Physikal. Z.*, 1935, **36**, 100, 193; *Chem. Reviews*, 1936, **19**, 171) and Fowler (*Proc. Roy. Soc.*, 1935, *A*, **149**, 1) have assumed that dipolar molecules in liquids are not free to rotate but only to execute oscillations about axes whose directions change slowly, but over short periods of time are fixed by the fields of the neighbouring molecules. Thus Debye writes for the orientation polarisation: ${}_{O}P = (4\pi N\mu^2/9kT)[1 - L^2(\beta)]$, where $L(\beta)$ is Langevin's function of $\beta = E/kT$. For sulphur dioxide we have ${}_{O}P_{\text{liq.}}/{}_{O}P_{\text{gas}} = 0{\cdot}5 = [1 - L^2(\beta)]$, whence E, the " binding energy " $= 3{\cdot}4kT$; for comparison, water shows ${}_{O}P_{\text{liq.}}/{}_{O}P_{\text{gas}} = 0{\cdot}193$ and $E = 11kT$, and ammonia, 0·41 and $4{\cdot}4kT$ respectively. The theoretical calculation of E has not yet been accomplished. Attempts, using the molecular interactions obtained by London (*Trans. Faraday Soc.*, 1937, **33**, 8) in conjunction with inter-dipole distances of $2r$, where $r^3 = 0{\cdot}916 \times$ molecular volume $\times 10^{-24}$, yield only $E = 0{\cdot}25kT$ for water and $0{\cdot}1kT$ for ammonia. A more serious objection is that the factor $[1 - L^2(\beta)]$ fails to deal with cases (*e.g.*, trimethylamine) where ${}_0P_{\text{liq.}}/{}_0P_{\text{gas}}$ exceeds unity.

Kincaid and Eyring (*J. Chem. Physics*, 1938, **6**, 620) have approached the problem *via* the " free volumes " and the " free angle ratios " (f.a.r.) of molecules in a condensed phase. Both these concepts, to a first approximation, concern the regions in which displacement can occur. For molecules with three degrees of freedom the f.a.r. is written δ_3 and the rotation taken as restricted between the limits of the polar angles 0 and θ_1, then $\mu^2_{\text{liq.}}/\mu^2_{\text{gas}} = 1 - [(1 + \cos\theta_1)/2]^2$. Since it is often approximately true that the potential curves for the rotation of the molecule about the three axes are symmetrical, $\delta_2 = \delta_3{}^{2/3}$ and $\delta_2 = (1 - \cos\theta_1)/2$. For the angular water molecule, $1/\delta_3$ is calculable from the product ($6{\cdot}1 \times 10^{120}$) of the principal moments of inertia and various constants as $10{\cdot}14 \times 10^{60} \times (ABC)^{\frac{1}{2}} = 25{\cdot}05$; δ_2 therefore is 0·116, whence $\mu^2_{\text{liq.}}/\mu^2_{\text{gas}} = {}_0P_{\text{liq.}}/{}_0P_{\text{gas}} = 0{\cdot}22$, *i.e.*, of the order found by direct measurement (0·19). A parallel calculation cannot yet be made for sulphur dioxide ($ABC = 13{\cdot}9 \times 83{\cdot}2 \times 97{\cdot}1 \times 10^{-120}$, Mulliken, *Rev. Mod. Physics*, 1942, **14**, 204) since the frequencies associated with hindered translation or rotation do not seem to have been observed (cf. Cartwright, *Nature*, 1935, **136**, 181; *Physical Rev.*, 1936, **49**, 470; Strong and Woo, *ibid.*, 1932, **42**, 267; for the Einstein functions in the water case just cited we have used $\nu = 170$ and 500 cm.$^{-1}$ from Hibben, " The Raman Effect and its Chemical Applications," Reinhold, 1939, p. 320).

The required $(\delta_3)_{SO_2}$ has therefore been estimated from the product δ_3V_f ($= \boldsymbol{R}T/p\,.\exp\Delta H_{\text{vap.}}/\boldsymbol{R}T$; Kincaid and Eyring, *loc. cit.*) and the equation : $(v_f)^{1/3} = 2\boldsymbol{R}TV^{0{\cdot}33}/N^{0{\cdot}33}\Delta E_{\text{vap.}}$ (Glasstone, Laidler, and Eyring, " Theory of Rate Processes," McGraw-Hill, 1941, p. 479), in which the symbols have conventional meanings or are defined in the sources cited; $T = 298°$; p, the vapour pressure of liquid sulphur dioxide at 298°, is 3·863 atm. (International Critical Tables, Vol. III, p. 236), the molecular volume, 46·8 (present paper), and the latent heat of evaporation 345 joules/g. (estimated from data given by International Critical Tables, Vol. V, p. 138). Thus $\delta_3 = 0{\cdot}03$ and $\delta_2 = 0{\cdot}097$, whence $\mu^2_{\text{liq.}}/\mu^2_{\text{gas}}$ should be *ca.* 0·2. This is 2·5 times too small. From the observed ratio, δ_2 is seen to be 0·29. Kincaid and Eyring note that δ_2 from dielectric constant measurements tends to exceed $(\delta_3)^{2/3}$ from other sources (*e.g.*, with methanol, $\delta_2 = 0{\cdot}25$ from ε methods and 0·13 by the alternative routes). Nevertheless the theory evidently fits the simple molecule sulphur dioxide too inadequately for it to merit the status of a general *a priori* explanation of solvent effects. In its present form it has the further disadvantage that it cannot forecast correctly those circumstances which lead to ${}_0P_{\text{liq.}}/{}_0P_{\text{gas}}$ ratios greater than one.

Concluding Remarks.—We have disregarded certain early empirical relationships, such as those proposed by Müller, Jenkins, Arkel and Snoek, Sugden, Henriquez, etc. (cf. Glasstone, *Ann. Reports*, 1936, **33**, 117 for summary and references) since they all required the ratio $\mu_{\text{liq. or soln.}}/\mu_{\text{gas}}$ to be less than unity—a forecast already adequately established as not always correct (*e.g.*, Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374; compare paraldehyde, following paper). The present work on sulphur dioxide has now demonstrated the inapplicability of a number of other treatments which have hitherto shown signs of sufficiency. The Ross-Sack theory alone remains with promise of explaining apparent moment ratios in dilute solutions. Even it will not cover pure polar liquids. Perhaps it is impracticable to hope for a " universal formula " in the latter problem. Indeed, as knowledge of liquid " structures " accumulates, the need for such a " formula " will decline, since the calculations necessary should then require only the ordinary considerations of electrostatics.

Materials not Specified Previously.—*Carbon tetrachloride.* Technical carbon tetrachloride was refluxed over mercury for 16 hours, then shaken for some hours successively with concentrated sulphuric acid, dilute sodium hydroxide solution, and water. After storage over calcium chloride for a week, it was fractionally distilled from paraffin wax, again dried (P_2O_5) for further week, redistilled, left over phosphoric oxide for 3 weeks, and distilled immediately before use, the middle half of the distillate (b. p. 76·7°) only being collected.

Toluene. Commercial toluene was shaken several times with small quantities of concentrated sulphuric acid and washed with dilute aqueous sodium hydroxide and distilled water; it was then dried ($CaCl_2$), refluxed for some hours over mercury, dried (P_2O_5) for a week, and redistilled; b. p. 110·6°.

Ether. To remove the chief impurities present in " B.P. " ether, it was shaken with $\frac{1}{10}$th of its volume of 10% silver nitrate solution (cf. Werner, *Analyst*, 1933, **58**, 335), washed with water, concentrated sulphuric acid, and water, dried (Na wire), fractionally distilled, dried, and again distilled; b. p. 34·6°.

Chloroform. An " AnalaR " supply was successively shaken with sodium hydrogen sulphite solution, water (twice), concentrated sulphuric acid (3 times) and water, dried ($CaCl_2$) for 3 weeks, distilled, dried (P_2O_5), and redistilled, b. p. 61·2°.

Ethyl bromide. Ethyl bromide (from B.D.H.) was shaken successively with concentrated sulphuric acid, sodium carbonate solution, and water (each 4 times, and for some hours). It was then dried

(CaCl$_2$), fractionally distilled, dried (P$_2$O$_5$), distilled again, and stored over phosphoric oxide, being distilled before use; b. p. 38·4°.

Ethylene dichloride. The commercial liquid was washed with dilute potassium hydroxide solution and water, dried (CaCl$_2$), distilled, and twice dried (over P$_2$O$_5$), and redistilled; b. p. 83·5°.

Acetone. This was shaken with a small quantity of 15% silver nitrate, to which had been added an equal volume of N-sodium hydroxide (Werner, *loc. cit.*). It was then dried (K$_2$CO$_3$), distilled, set aside over potassium carbonate, and redistilled before use. This specimen was still sufficiently moist to damp the oscillations appreciably; a further rapid distillation over phosphoric oxide failed to bring about an adequate improvement; b. p. 56·3°.

Benzene. "AnalaR" thiophen-free benzene was dried over sodium wire, purified twice by fractional crystallisation, and stored over sodium wire.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, September 12th,* 1949.]

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61. *The Dielectric Polarisations of Liquid, Dissolved, and Gaseous Paraldehyde.*

By R. J. W. LE FÈVRE, (MISS) J. W. MULLEY, and B. M. SMYTHE.

New measurements now recorded show paraldehyde to have a larger apparent moment in the liquid (1·7$_3$ D.) or dissolved states (light petroleum, 1·7$_7$; dioxan, 1·9$_0$; carbon tetrachloride, 1·9$_8$; benzene, 1·8$_7$; chloroform, 2·1$_4$) than as a gas (1·44). The last datum follows from the equation: $_{T}P = 44\cdot47 + 12792/T$. The ratios $\mu_{\text{liq.}}/\mu_{\text{gas}}$ or $\mu_{\text{soln.}}/\mu_{\text{gas}}$ are the greatest yet recorded.

These results are discussed in relation to extant theories for the role of the medium in dipole moment measurements.

The atomic polarisation of paraldehyde is approximately one-third of the electronic.

THE present communication extends an earlier one by Le Fèvre and Russell (*J.*, 1936, 496), in which paraldehyde was examined merely because it had a large negative Kerr constant. During the intervening thirteen years, however, its molecular dimensions have been established (Ackerman and Mayer, *J. Chem. Physics*, 1936, **4**, 377; Brockway and Carpenter, *J. Amer. Chem. Soc.*, 1936, **58**, 1270; Gerding *et al.*, *Rec. Trav. chim.*, 1939, **58**, 604, 615; 1941, **60**, 258). Its shape allows it credibly to be fitted within an ellipsoid of rotation about the resultant dipole moment as axis (cf. Calderbank and Le Fèvre, *J.*, 1949, 199). Paraldehyde becomes accordingly an attractive "model" upon which to test extant theories for the variation of apparent polarisation and state.

Le Fèvre and Russell (*loc. cit.*) recorded dielectric constant and density figures for the pure liquid and solution of it in nine solvents, but fearing the presence of the equilibrium, C$_6$H$_{12}$O$_3$ = 3CH$_3$·CHO, refrained from proceeding to a discussion. It is now clear that this anxiety was unjustified, since in ordinary organic media depolymerisation becomes marked only in the presence of acid catalysts (Orton and McKie, *J.*, 1917, **109**, 185; Bell, Lidwell, and Vaughan-Jackson, *ibid.*, 1936, 1792). Moreover, in 1936 the necessary polarisation data for the gaseous state were lacking; the provision of these, together with a number of recent or repeated results in various solvents, is the main object of this paper.

The total molecular polarisation of paraldehyde vapour as a function of the absolute temperature has been found to follow the equation: P (c.c.) $= 44\cdot47 + 12792/T$, whence $\mu = 1\cdot44$ D., and the electronic and atomic contributions together (44·47 c.c.) are seen to exceed the $[R_L]_D$ value (33·1 c.c.) used by Le Fèvre and Russell.

Further, where dissolved paraldehyde is concerned, our additional determination in benzene, light petroleum, and dioxan make it evident that rectilinear relationships do not hold between concentration (as weight fraction, w_1) and either the dielectric constants (ε_{12}) or the densities (d_{12}) of the mixtures (compare Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). With trioxymethylene and trithioformaldehyde, signs of the same phenomenon were found by Calderbank and Le Fèvre (*J.*, 1949, 199). Accordingly both our new measurements in non-polar solvents and those from Le Fèvre and Russell (relating to carbon tetrachloride and chloroform) have been evaluated or recalculated (cf. Le Fèvre, *loc. cit.*) to allow for this effect. The figures so produced are set out in Table I, which includes, for comparison, certain others (under μ^*) previously given in 1936, together with those (under μ_R) obtained by the refractivity method.

TABLE I.

Apparent moment and polarisation of paraldehyde at 25°.

Solvent or state.	Total pn.	Orientn. pn.	μ^*, D.	μ_R, D.	μ, D.
Gas	87·40	$42·9_3$	—	$1·6_2$	1·44.
Light petroleum	$109·0_2$	$64·5_5$	—	$1·9_2$	1·77
Dioxan	$119·2_6$	$74·7_9$	—	$2·0_4$	1·90
Carbon tetrachloride	$125·7_3$	$81·2_6$	$2·1_2$	$2·1_2$	1·98
Benzene	$117·0_3$	$72·5_6$	$2·0_3$	$2·0_1$	1·87
Chloroform	$139·4_6$	$94·9_9$	$2·2_6$	$2·2_7$	2·14
Pure liquid	106·6	62·1	$1·8_9$	$1·8_9$	1·73

Le Fèvre and Russell (*loc. cit.*) also list apparent polarisations in six polar solvents, but the significance of these is doubtful (cf. Glasstone, *Ann. Reports*, 1936, **33**, 134). The questions underlying such measurements, and those of Le Fèvre and Le Fèvre (*J.*, 1936, 487), are now being re-examined on a wider basis in this Department. Where paraldehyde is concerned, therefore, we wish, at this stage, to restrict consideration to the data of the above table, chloroform being retained because it has sometimes been thought admissible as a medium for dipole moment work (cf. Le Fèvre and Rayner, *J.*, 1938, 1921; Caldwell and Le Fèvre, *J.*, 1939, 1614; Calderbank and Le Fèvre, *J.*, 1949, 1462; and the Faraday Soc. List of Dipole Moments, 1934).

Discussion.—The true moment, as determined for the gaseous phase, is surprisingly lower than the apparent moments shown in solution or the liquid state. Paraldehyde is known to undergo spontaneous depolymerisation on heating (Coffin, *Canad. J. Res.*, 1932, **7**, 75; Dacey and Coffin, *J. Chem. Physics*, 1937, **7**, 315), but from the kinetic study of Burnett and Bell (*Trans. Faraday Soc.*, 1938, **34**, 420) it is evident that even at 261° the time of half-change is *ca.* 31 minutes, while below 210° the pressure changes (used as indexes to reaction rates) were scarcely measurable (Coffin, *loc. cit.*). Accordingly, by confining our experiments to temperatures below 200°, and adhering to the timing already specified (Le Fèvre, Ross, and Smythe, *J.*, 1950, 276), we believe we have not incorrectly attributed the observed polarisations to paraldehyde alone, rather than to a changing system, $C_6H_{12}O_3 \rightleftharpoons 3CH_3{\cdot}CHO$.

In terms previously used (Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374; Le Fèvre and Ross, *J.*, 1950, 283) we may summarise the facts thus:

	Light petroleum.	Dioxan.	CCl_4.	C_6H_6.	$CHCl_3$.	Liquid.
$\mu^2_{\text{liq.}}/\mu^2_{\text{gas}}$	1·51	1·74	1·90	1·69	2·22	1·45
$\Delta\mu/\mu_{\text{gas}}$	+0·23	+0·32	+ 0·37	+0·30	+0·49	+0·20

Since the media have been arranged with increasing dielectric constants from left to right, it is obvious that none of the treatments of the " solvent effect " problem in which ε is the controlling factor can be valid for paraldehyde. On the other hand, those theories which involve the shape of the solute, or the algebraic sign of its Kerr constant, appear—qualitatively at least—to be more successful; indeed the $\mu_{\text{liq.}}/\mu_{\text{gas}}$ ratio now found, although higher than any other yet recorded in the literature, can be roughly forecast by applying Higasi's expressions (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1936, **28**, 284) as though they were intended for polar, as well as non-polar, solvents. Carpenter and Brockway (*loc. cit.*) assign paraldehyde to the first of four models illustrated in their paper. In this, the three oxygen atoms are approximately coplanar with the three methyl-carbon atoms; and these six are 0·47 A. above a parallel plane containing the remaining carbon atoms; C–O and C–C distances of 1·43 and 1·54 A. are also given. All intervalency angles are tetrahedral. A scale drawing of the " elevation " of this skeleton (through one of the oxygens and its opposite CH–Me), after adding outlines corresponding to van der Waals radii, shows that rotation about the direction of action of the resultant moment (cf. Calderbank and Le Fèvre, *loc. cit.*) requires a somewhat flat spheroidal cavity. Several may be drawn but the axial ratios $a : b : c$ are consistently about $\frac{1}{2} : 1 : 1$. Following Higasi, therefore, $k = 2$ in $B = k^2(k^2 - 1)^{-1}\{1 - (k^2 - 1)^{-\frac{1}{2}} \sin^{-1}(k^2 - 1)^{\frac{1}{2}}/k\} - 1/3$, whence $B = 0{\cdot}195$ and $\Delta\mu(= 4\pi\alpha n\mu_{\text{gas}}B$, where n and α represent the number of molecules of medium per unit volume and their polarisability respectively) $= 0{\cdot}20 \times 10^{-18}$ e.s.u. Thus the calculated value of $(\mu^2_{\text{liq.}}/\mu^2_{\text{gas}})$ is 1·30 compared with the 1·45 actually recorded. Further, of course, the fact that ${}_{O}P_{\text{liq.}}/{}_{O}P_{\text{gas}}$ exceeds unity is compatible with θ (in expressions derived from the equation of Raman and Krishnan, *Proc. Roy. Soc.*, 1928, *A*, **117**, 589) having a positive sign, *i.e.*, the reverse of that of the Kerr constant. In view, however, of considerations prompted by the case of sulphur dioxide (*J.*, 1950, 286), this particular aspect will not be pursued.

According to Onsager (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) the true orientation polarisation of a substance should be $(\varepsilon - n^2)(2\varepsilon + n^2)V/\varepsilon(n^2 + 2)^2$, where V = molecular volume and n is the refractive index for light of infinite wave-length, V and n referring to the condensed phase. Frequently (cf. Böttcher, *Physica*, 1939, **6**, 59; Le Fèvre, Smythe, and Roberts, *J.*, 1949, 902) the use of n_D in place of n_{∞} makes only a small difference. Wilson (*Chem. Reviews*, 1939, **25**, 377) recommends that $n_{\text{effective}}$, calculated from the distortion polarisation, be adopted instead. With paraldehyde either route gives an extremely high figure: (*a*) n^2_D = 1·989, from $[R_L]_D$ = 33·1, $({}_OP)_{\text{calc.}}$ = 198 c.c. at 25°; (*b*) $n^2_{\text{eff.}}$ = 2·499, from $({}_AP + {}_EP)$ = 44·47, $({}_OP)_{\text{calc.}}$ = 151 c.c. at 25°; ${}_OP$, calc. *via* ${}_TP = 44{\cdot}47 + 12792/T$ (cf. p. 290) = 43 c.c. at 25°. Looking over Böttcher's examples, it seems that molecules of the type possessing negative Kerr constants are least satisfactorily handled by the unmodified Onsager formula. (Paraldehyde provides the worst instance to date in our experience.) Onsager, however, was well aware of the limitations imposed by his choice of simplifying and preliminary assumptions (cf. Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43** 391—392). Modifications, giving recognition to the optical anisotropy of the solute, in the manner indicated by Wilson (*loc. cit.*), would certainly improve the situation, but unfortunately neither electric double refraction nor light-scattering studies for gaseous paraldehyde have been made.

With regard to Kirkwood's extension of Onsager's equation (*J. Chem. Physics*, 1939, **7**, 911; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 315), *viz.*, $M(\varepsilon - 1)(2\varepsilon + 1)/9\varepsilon d = {}_EP + {}_AP + 4\pi N\mu^2 g/9kT$, we note (since M/d = 133·5 c.c. and ε_{25} = 12·934; Le Fèvre and Russell, *loc. cit.*) that g is approximately 7·5. This is large (cf. preceding paper for other examples) and would appear to indicate a small value of $(\cos\gamma)_{\text{average}}$ in $g = 1 + Z(\cos\gamma)_{Av}$, where Z is the number of molecules in the first layer around the one under consideration. If Z were about six, and all seven molecular resultant dipoles moving about axes not far from parallel, a model is seen in which maximum "contact" of molecular "areas" is tending to occur. It is relevant to mention, however, that cryoscopically (see following paper) there is no evidence that paraldehyde is "associated" in the ordinary sense of the word.

Finally, the theories based on hindered rotation (*e.g.*, those of Debye, or Kincaid and Eyring, see preceding paper) cannot be applied to paraldehyde, for which ${}_OP_{\text{liq.}}/{}_OP_{\text{gas}}$ is 1·45, since—as was pointed out *a propos* sulphur dioxide—a ratio greater than unity is made impossible by the mathematical forms by which their authors expressed them.

The above paragraphs are chiefly concerned with the *liquid*–gas relationship. We are indebted to Mr. I. G. Ross for some remarks on paraldehyde as a *solute*: using as axes for the spheroid those quoted before (namely 0·5 : 1·0 : 1·0) the Ross–Sack equation is

$$\mu_{\text{soln.}}/\mu_{\text{gas}} = 3\varepsilon[1 + (n^2_{\text{eff.}} - 1)\xi]/(\varepsilon + 2)\,[\varepsilon + (n^2_{\text{eff.}} - \varepsilon)\xi] \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where in this case $\xi = (1/e^2) - [(1 - e^2)^{\frac{1}{2}}/e^3]\sin^{-1}e = 0{\cdot}527$, and $e = [1 - (a/b)^2]^{\frac{1}{2}}$. For comparison, the Higasi equation for solutions may be written as

$$\mu_{\text{soln.}}/\mu_{\text{gas}} = 1 + 3(\xi - 1/3)(\varepsilon - 1)/(\varepsilon + 2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

although it is suggested that the derivation of (2) contains errors and that, with Higasi's approach, the correct form should be

$$\mu_{\text{soln.}}/\mu_{\text{gas}} = 1 + (\xi - 1/3)\varepsilon/(\varepsilon + 2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The apparent moments in solution, calculated by (1), (2), and (3), are compared below with those actually recorded:

Solvent.	μ, observed.	μ, calc. by (1).	μ, calc. by (2).	μ, calc. by (3).
Vacuum	$1{\cdot}4_4$	—	—	—
Light petroleum	$1{\cdot}7_7$	$1{\cdot}7_1$	$1{\cdot}6_5$	$1{\cdot}5_8$
Dioxan	$1{\cdot}9_0$	$1{\cdot}7_2$	$1{\cdot}6_8$	$1{\cdot}5_9$
Carbon tetrachloride	$1{\cdot}9_8$	$1{\cdot}7_2$	$1{\cdot}6_8$	$1{\cdot}5_9$
Benzene	$1{\cdot}8_7$	$1{\cdot}7_2$	$1{\cdot}6_9$	$1{\cdot}5_9$

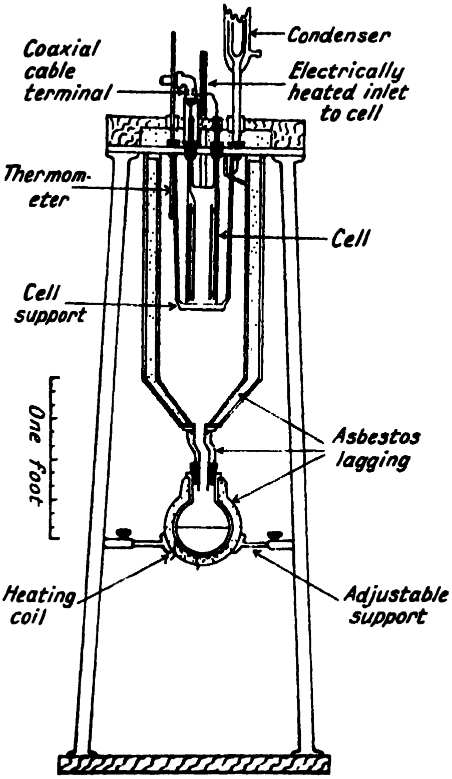
Equation (1) thus gives slightly better results than does that of Higasi, either in its original (2) or its amended (3) form.

Conclusions.—Paraldehyde is established as a case where the apparent moment, as ordinarily measured in solution *via* the Debye–Clausius–Mosotti route, is markedly greater than the true moment obtained from the gas. The facts now revealed, while out of harmony with many of the extant theoretical treatments of the problem, are less so with those in which the anisotropy of molecular shape (or polarisability) is significant.

EXPERIMENTAL.

Materials.—The paraldehyde was purified by drying it with anhydrous sodium sulphate and then cooling it to 5°, whereafter the frozen material was separated by decantation. This was distilled (the fraction, b. p. 121—124°, being collected), stored over anhydrous sodium sulphate for several days, and redistilled at atmospheric pressure before use as required.

Polarisation of Gaseous Paraldehyde.—The method of measurement has been essentially that described previously (*J.*, 1950, 276, apparatus B.M.S.) but with the following improvements. The gas cell was replaced by another of similar construction of 124 instead of 80 μμF. capacity (with air). Its leads were brought through the glass walls and soldered directly to the co-axial cable running to the oscillator. For the oil-thermostat, which had been a source of unsteadiness at higher temperatures (due to surface ripples made by the stirrer as the fluid became hotter and more mobile), an all-metal vapour bath, standing on the floor, was substituted. Its details are given in the figure. It had advantages over the glass apparatus of Groves (*J.*, 1939, 1147) in that it was more robust and formed a complete shield, which could be earthed, around the cell. The whole structure was heavily lagged to minimise heat radiation to the electrical components. By the use of chloroform, carbon tetrachloride, xylene, *n*-butyl alcohol, *cyclo*hexanol, benzyl alcohol, and thymol separately at atmospheric pressure, the temperature of the cell could easily be set to within 0·2° or better. The condensates ran back along a guide to flow down the inside wall of the vessel. The rate of boiling was controlled by adjusting the voltage across the heating coil by means of a "Variac" variable transformer.



The new cell was first calibrated against carbon dioxide (see p. 281). Table II shows the values obtained for $\delta C/p$, while the polarisations of paraldehyde follow in Table III.

TABLE II.

$\delta C/p$ for carbon dioxide.

$T°$, K.	$10^6/T$.	$\delta C/p$.	$(\delta C/p)_{\text{calc.}}$.	Press. range in cm.	Number of observations.
296·5	3372	7·66	7·662	34—68	10
333·5	2999	6·80	6·800	32—68	13
383·0	2611	5·91	5·905	38—67	13
404·0	2475	5·59	5·592	42—69	11
422·5	2367	5·34	5·342	35—67	12

Whence $x' = (2307{\cdot}0/T) - 0{\cdot}1185$.

TABLE III.

Paraldehyde.

$T°$, K.	$10^6/T$.	$(\delta C/p)_{p=0}$.	P (c.c.).	P (calc.).	Press. range in (cm.).	No. of observations.
386	2591	39·0	77·59	77·61	34—53	13
406	2463	36·2	75·71	75·98	29—61	12
437	2288	32·9	74·08	73·74	25—67	12
457	2188	31·0	71·24	72·46	16—52	11
390 *	2564	61·15	77·4	77·27	25—51	7
473 *	2114	46·00	71·54	71·51	23—56	6

Whence $P = 44{\cdot}47 + 12792/T$ and $\mu = 1{\cdot}44$ D.

Polarisation of Dissolved Paraldehyde.—Apparatus, techniques, and symbols used have been described before (*J.*, 1948, 1949). The solvents were fractionated (after partial freezing where applicable) and kept over sodium (except carbon tetrachloride, for which calcium chloride was used). The dielectric constants of light petroleum and of dioxan were determined relatively to benzene (2·2725).

The dielectric constants (ε^{25}), densities (d_4^{25}), and concentrations (w_1 = weight fraction) are alone recorded, since the polarisations at infinite dilution do not require the separate evaluation of these quantities for each solution (cf. Le Fèvre, *loc. cit.*) :

(a) *Paraldehyde in light petroleum* (*b. p.* 94—99°).

0^6w_1	0	9701	19036	38479	57468	79183
ε^2	1·9944	2·0158	2·0383	2·0872	2·1376	2·1969
$^{25}_{4}$	0·74062	0·74212	0·74367	0·74694	0·75023	0·75399

(b) *Paraldehyde in dioxan.*

0^6w_1	0	11221	15414	23323	40590	46453	54439
^{25}	2·2172	2·2607	2·2770	2·3086	2·3790	2·4017	2·4347
d_4^{25}	1·02917	1·02883	1·02863	1·02829	1·02762	1·02744	1·02703

(c) *Paraldehyde in carbon tetrachloride.*

10^6w_1	0	11545	19250	49053	72066	108066
ε^{25}	2·2270	2·2986	2·3457	2·5331	2·6733	2·8920
d_4^{25}	1·58440	1·57338	1·56628	1·53745	1·51644	1·48515

(d) *Paraldehyde in benzene.*

10^5w_1	0	493	1029	3424	3482	4522	4765	6467
ε^{25}	2·2725	2·2881	2·3044	2·3818	2·3832	2·4159	2·4243	2·4802
d_4^{25}	0·87378	0·87410	0·87440	0·87697	0·87750	0·87804	0·87840	0·87996
10^5w_1	7392	8863	9989	10777	12868	16481	20897	
ε^{25}	2·5079	2·5674	2·6027	2·6358	2·7159	2·8586	3·0392	
d_4^{25}	0·88082	0·88223	0·88342	0·88412	0·88603	0·88962	0·89417	

(e) *Paraldehyde in chloroform.*

10^5w_1	0	1098	3028	5389	8870	15528
ε^{25}	4·7240	4·8459	5·0617	5·3293	5·7204	6·4533
d_4^{25}	1·46814	1·46080	1·44803	1·43258	1·41078	1·36987

From the above measurements the " constants," $\alpha\varepsilon_2$ and βd_2 [*i.e.*, $(\varepsilon_{12} - \varepsilon_2)/w_1$ and $(d_{12} - d_2)/w_1$] show a drift with w_1. By least squares, the following relationships have been fitted:

Solvent.	No. of solns. and w_1-% range.	$\alpha\varepsilon_2$.	βd_2.
Light petroleum	5 (1—8%)	$2·204 + 4·76w_1$	$0·1552 + 0·004w_1$
Dioxan	6 (1—5·4%)	$3·850 + 2·83w_1$	$0·0316 + 0·147w_1$
Benzene	14 (0·5—21%)	$3·067 + 2·78w_1$	$0·0818 + 0·117w_1$
Carbon tetrachloride	5 (1—11%)	$6·207 - 0·30w_1$	$0·293w_1 - 0·9582$
Chloroform	5 (1—15%)	$11·19 \pm 0·0w_1$	$0·294w_1 - 0·6720$

Using the above data at $w_1 = 0$, the polarisations at infinite dilution listed in Table I are calculated as ${}_{\infty}P_1 = M_1[p_2(1 - \beta) + C\alpha\varepsilon_2]$, the requisite values of C and p_2 being :

	Light petroleum.	Dioxan.	Carbon tetrachloride.	Benzene.	Chloroform.
C	0·25388	0·16390	0·10597	0·18809	0·37724
p_2	0·33614	0·28045	0·18321	0·34086	0·04520

Note on the Atomic Polarisation of Paraldehyde.—Since the difference between the distortion polarisation (44·5 c.c.) and the molecular refraction (about 33 c.c.) is *ca.* 11 c.c., paraldehyde must be added to the growing list of cases which disprove the earlier idea that ${}_{A}P$ might be taken as approximately 10% of ${}_{E}P$. Coop and Sutton (*J.*, 1938, 1280) and Watson, Kane, and Ramaswamy (*Proc. Roy. Soc.*, 1936, *A*, **156**, 130) have provided the most striking instances. The relative position of the present observations can be seen from the following series of ${}_{A}P/{}_{E}P$ ratios :

p-Benzoquinone	0·29	(Coop and Sutton, *loc. cit.*)
p-Dinitrobenzene	0·21	,, ,, ,,
Beryllium acetylacetonate	0·42	,, ,, ,,
Ferric ,, ...	0·60	,, ,, ,,
Boron trifluoride	0·46	(Watson, Kane, and Ramaswamy, *loc. cit.*)
Carbon tetrafluoride	0·39	,, ,, ,,
Silicon tetrafluoride	0·65	,, ,, ,,
Cyanogen	0·70	,, ,, ,,
Paraldehyde	0·33	(Present work.)

Comparison with data for a number of ethers is interesting :

	Me_2O.	Et_2O.	Dioxan.	Trioxan.	Paraldehyde.
${}_{\mathrm{A}}P$	2·2	4·0	3·0	*ca.* 13 *	11·4
${}_{\mathrm{E}}P$	12·9	21·9	21·6	19·3	33·1

* Calculated from the dielectric constant of solid trioxan at 20° (Walker and Carlisle, *Chem. Eng. News*, 1943, **21**, 1250), *viz.*, $\varepsilon = 3{\cdot}2 - 3{\cdot}4$ at 1·6 megacycles. The value of d^{20} is not given ($d_4^{65} = 1{\cdot}17$), but has been taken as 1·2 since a higher figure would not appreciably affect $M(\varepsilon - 1)/(\varepsilon + 2)d = 32$ c.c.

That the three cyclic molecules have similar configurations follows from (*a*) the structural details for paraldehyde recorded by authors cited at the beginning of this paper, (*b*) investigations of crystal structure (Moermann, *Rec. Trav. chim.*, 1937, **56**, 161), dipole moment (Maryatt and Acree, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 71; Calderbank and Le Fèvre, *J.*, 1949, 199), infra-red (Ramsay, *Trans. Faraday Soc.*, 1948, **44**, 289) and Raman spectra (Kohlrausch, *Z. physikal. Chem.*, 1937, *B*, **35**, 29) on trioxan, and (*c*) studies of electron diffraction (Brockway and Sutton, *J. Amer. Chem. Soc.*, 1935, **57**, 473) and infra-red and Raman spectra (Ramsay, *Proc. Roy. Soc.*, 1947, **190**, 563) on dioxan. Oxygen bond angles and C–O distances, where given, are of the same order throughout (*viz.*, 110° ± 5°, and 1·43—1·46 A.) and closely resemble those for dimethyl ether (Brockway and Sutton, *loc. cit.*).

From Sutton's theory of atom polarisation (see p. 283 for references) it follows that: (1) since this quantity depends on polar groups in a molecule whereas ${}_{\mathrm{E}}P$ does not, ${}_{\mathrm{A}}P$ cannot be expected to be always the same fraction of ${}_{\mathrm{E}}P$; (2) if several compounds have essentially common oscillating systems, they have nearly the same ${}_{\mathrm{A}}P$; and (3) in general ${}_{\mathrm{A}}P$ is not additive, but in some circumstances (if μ and V_{O}, in ${}_{\mathrm{A}}P = 4\pi N\mu^2{}_1/9V_{\mathrm{O}}$, are constant) it is roughly proportional to the number of polar bonds, or components.

The figures just quoted illustrate these propositions. The ${}_{\mathrm{A}}P/{}_{\mathrm{E}}P$ fraction for paraldehyde is not that for many other molecules, although the absolute value of its ${}_{\mathrm{A}}P$ seems to be of the order of that of trioxan. The angular force constants, V_{O}, for bending of C–O–C in dimethyl ether and in dioxan are 0·34—0·46 and 0·66 × 10^5 dynes/cm. respectively (Kohlrausch, *loc. cit.*; Bonner, *J. Chem. Physics*, 1937, **5**, 293); since ${}_{\mathrm{A}}P = 4\pi Nn\mu^2{}_1/9V_{\mathrm{O}}$ (where n = the number of oscillating components, *i.e.*, 1 for dimethyl ether and 2 for dioxan), the atomic polarisations for these two molecules should be approximately the same, as in fact they are.

The deformation constants of the C–O–C angles in paraldehyde and trioxan have not been determined. However, Ramsay (*Trans. Faraday Soc.*, 1948, **44**, 289) attempted to calculate the vibration frequencies of the trioxan ring using the same values for the force constants as for dioxan, but differences between his estimates and those observed are large, and indicate that the force constants in trioxan are appreciably smaller than those in dioxan. Nevertheless, if the bending force constant of C–O–C in trioxan (which as a first approximation should be of the same order as that for paraldehyde, as are the C–O bond distances and the C–O–C angles) is closer to that of dimethyl ether, then we would expect an atomic polarisation approaching three times that of dimethyl ether, or 9 c.c. This is in effect the situation found. These results shown the degree of additivity of ${}_{\mathrm{A}}P$ in these compounds. It resembles that which has also been noticed with certain polyhalides and the metal acetylacetonates (Finn and Sutton, *J.*, 1938, 1259; Coop and Sutton, *loc. cit.*).

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA.

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62. *The Apparent Polarisations of Paraldehyde in Non-polar Solvents Measured at* 10 *and* 25 *cm.*

By R. J. W. LE FÈVRE and (MISS) J. W. MULLEY.

Direct observation has verified that, where the common non-polar solvents of low (centipoise order) viscosity are concerned, the results of the preceding paper are not due to a spectrum of relaxation times reaching into the 300-m. region. Signs of dispersion of orientation polarisation may be seen between 25 and 10 cm., but this is credibly reconcilable with the simple Debye formula and accepted molecular dimensions. Solutions of paraldehyde in medicinal paraffin (viscosity *ca.* 0·2 poise) have also been investigated.

THE measurements recorded in this communication were made for precautionary reasons. The time, τ (seconds) of molecular relaxation in a dielectric is given by the well-known equation of Debye as $\tau = 4\pi\eta r^3/kT$, where η is the macro-viscosity (poises), r is the molecular radius (cm.), k is Boltzmann's constant ($1{\cdot}37 \times 10^{-16}$ ergs/degree), and T is the absolute temperature. If f represents the frequency (in c./s.) of the applied alternating field which corresponds to τ (through the relation $\tau = 1/2\pi f$) we have : $fr^3 = kT/8\pi^2\eta$. Now, the viscosities of the solvents used in the previous work range from 0·2 to 2·0 centipoises. At 25°, therefore, the product fr^3 should be between $2{\cdot}5 \times 10^{-13}$ and $2{\cdot}5 \times 10^{-14}$. Fig. 1 illustrates the consequent dependence of f upon r.

Assuming paraldehyde to be a liquid composed of close-packed spheres, r may be calculated as $0{\cdot}665V^{1/3} \times 10^{-8}$ cm. (V = molecular volume), *i.e.* (since $d_4^{20} = 0{\cdot}990$), 3·40 A. Its viscosity at 20° is 1·18 centipoises (Muchin, *Z. Elektrochem.*, 1913, **19**, 820). Accordingly, if this solute exists in the pure state or in dilute solution (of the type customarily used for dipole moment measurements), as single molecules, its orientation polarisation (${}_OP$) should remain constant until the applied frequency approaches 10^9 c.p.s., *i.e.*, a figure safely distant from that (10^6 c.p.s.) utilised in the preceding paper.

FIG. 1.

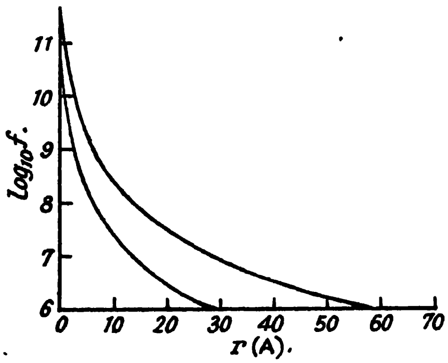
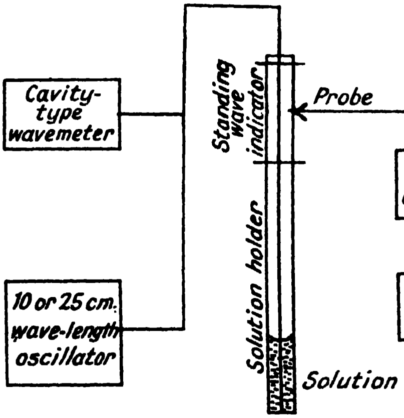


FIG. 2.



However, note should be taken of the following facts : the simple expression of Debye, implying spherical molecules freely rotating against one another and a single relaxation time, is too idealised. It indicates only the *order* of results obtained by direct experiment (cf. Holzmuller, *Physikal. Z.*, 1937, **38**, 574). Most molecules, in fact, would be more accurately regarded as ellipsoids with three axes, for which three values of τ should be foreseen *a priori* (Perrin, *J. Phys. Radium*, 1934, **5**, 497). In at least one instance (Girard and Abadie, *Faraday Soc. Discussion*, 1946, **42**, *A*, 40) dilution has revealed a plurality of dispersion regions. The coefficient of viscosity of flow is only a rough measure of the coefficient of internal friction really required by the Debye relation; for equal concentrations of the same solute in different solvents, maximum dielectric absorption does *not* occur at identical viscosities (Hall, Halliday, Johnson, and Walker, *ibid.*, p. 136). There are indications that the variations are connected with the shapes of the solvent molecules (Thompson, *ibid.*, p. 160). With benzophenone in benzene the incremental loss tangent is still diminishing as f descends past 10^8 c.p.s. (Jackson and Powles, *ibid.*, p. 106); with medicinal paraffin as solvent (η = 1·97 poises) the corresponding point appears to be 10^6 c.p.s.—suggesting the presence of a spectrum of relaxation times.

Now, although cryoscopic studies (Paterno and Nasini, *Ber.*, 1886, **19**, 2529; Luginin and Dupont, *Bull. Soc. Chim.*, 1911, [iv], **9**, 223) in a few solvents have shown paraldehyde to be monomeric, there is still the possibility that in its dielectric behaviour it may act effectively either as double, treble, etc., units (through association, of the cybotactic type with itself) or as a lose structure carrying an " atmosphere " of solvent molecules. Were such to be the case a lower f should follow the greater r. In addition to other uncertainties already mentioned we cannot be sure that the variations of ${}_OP$ just reported have been of the kind we set out to study.

To delimit the possible existence of a similar " spectrum " with paraldehyde we have explored the effects of changing (*a*) the viscosity of the solvent or (*b*) the wave-length of measurement. In the following table we compare our results with those of the preceding paper :

Solvent.	Viscosity, poise.	Wave-length.	$({}_{\infty}P_1)_{25}$, c.c.
Light petroleum	*ca.* 0·003	*ca.* 300 m.	109
Medicinal paraffin	*ca.* 0·2	,,	124—125
Benzene	*ca.* 0·006	,,	117
,,	,,	25 cm.	113—124
,,	,,	10 cm.	102—107

The first two lines show that despite a 60—70-fold increase of viscosity, the total polarisation of paraldehyde is not diminished. It is similarly apparently unaffected by a change of measuring frequency from 10^6 c.p.s. (300 m.) to $1{\cdot}2 \times 10^9$ c.p.s. (25 cm.). The reduction recorded at $0{\cdot}3 \times 10^{10}$ c.p.s. (10 cm.) *may*, however, be real since (i) it appeared also at finite concentrations whenever the same solution was successively examined at the two shortest wave-lengths, and (ii) it leads to reasonable estimates for the relaxation time: if ${}_{\mathrm{T}}P_{\mathrm{obs.}} = 4\pi N[\alpha + \mu^2/3kT(1 + j\omega\tau)]/3$, then $j\omega\tau = ({}_{\mathrm{T}}P_{\mathrm{L}} - {}_{\mathrm{T}}P_{\mathrm{obs.}})/({}_{\mathrm{T}}P_{\mathrm{obs.}} - {}_{\mathrm{D}}P)$, where ${}_{\mathrm{T}}P_{\mathrm{obs.}}$ and ${}_{\mathrm{T}}P_{\mathrm{L}}$ are respectively the total polarisations observed at angular frequencies, ω, such that for the former $\omega\tau$ is not negligible, ${}_{\mathrm{D}}P$ is the distortion polarisation (44·5 c.c. for paraldehyde, cf. preceding paper), and τ is the relaxation time (defined as $\omega\tau = 1$). From our data at 300 m. and 10 cm. (above), $j\omega\tau$ lies between 0·16 and 0·26, whence $T_{25} = 8$—14×10^{-12} secs. That τ is of such an order seems possible from comparison with recorded values for other molecules, *e.g.*, camphor $6{\cdot}2 \times 10^{-12}$ secs. (in *cyclo*hexane at 30°; Whiffen, *J. Amer. Chem. Soc.*, 1948, **70**, 2452), chloroform $7{\cdot}7 \times 10^{-12}$ secs. (in benzene at $19° \pm 1°$; Jackson and Powles, *Trans. Faraday Soc.*, 1946, **42**, *A*, 101), or acetone $3{\cdot}2 \times 10^{-12}$ secs. (in benzene at $19° \pm 2°$; Whiffen and Thompson, *ibid.*, p. 118).

We conclude, therefore, that the variations of polarisation registered at 300 m. (preceding paper) are due to solvent influences and not to dispersion effects.

EXPERIMENTAL.

Measurements in Medicinal Paraffin.—The solvent was a commercial sample which had been stored over clean sodium wire for 2 days. It was used without further purification. Procedures followed our standard practice (cf. *J.*, 1948, 1949, and preceding papers, wherein the symbols used below are defined). Results are shown in the following table:

10^5w_1.	ε^{25}.	d_4^{25}.	P_1 (c.c.).	10^5w_1.	ε^{25}.	d_4^{25}.	P_1 (c.c.).
0	2·1467 *	0·8510	—	3964	2·2720	0·8543	121·3
2297	2·2193	0·8530	123·0	4435	2·2870	0·8549	121·5

* By direct comparison with benzene, $\varepsilon^{25} = 2{\cdot}2725$.

From these, the maximum and minimum values for $\alpha\varepsilon_2$ are 3·18 and 3·16, and for βd_2 0·0884 and 0·0845, whence ${}_{\infty}P_1 = 124$—125 c.c.

Measurements at 25 *and* 10 *cm.*—These have been made on co-axial equipment, the generators being a cavity tuned lighthouse triode oscillator and a reflex klystron respectively. A general outline of the apparatus is given in Fig. 2. Standard 5/8″ internal diameter, 51 ohm impedance transmission line was used for both the solution holder and the standing wave indicator (the latter was a U.S. War Dept. Type TS-56A/AP model).

The waves are propagated down the line, reflected up through the liquid from the short-circuited end, and the positions of voltage minima of the standing waves, with various depths of liquid in the line, are determined. By plotting the depth of liquid in the line against the distance of the minimum from the surface of the liquid, the wave-length in the liquid can be found. The apparent dielectric constant then follows as $(\lambda_{\mathrm{air}}/\lambda_{\mathrm{soln.}})$.

Since, in general, solutions were made up on different occasions and examined relatively to air—and not the pure solvent, as in ordinary dipole moment work—a separate determination of $\varepsilon_{\mathrm{C_6H_6}}$ was also made in each case. Hence in the following table, the magnitudes of C $[= 3/d_2(\varepsilon_2 + 2)^2]$ and p_2 $[=(\varepsilon_2 - 1)/\mathrm{d}_2(\varepsilon_2 + 2)]$ are not shown as the same for all solutions:

Paraldehyde in benzene.

	Wave-length = 10 cm.			Wave-length = 25 cm.		
10^5w_1	1029	3482	4765	1029	3482	4765
Temp.	23·0°	21·5°	21·3°	22·4°	22·0°	22·0°
d_4^t	0·8771	0·8813	0·8824	0·8774	0·8809	0·8815
$(p_2)^t$	0·3306	0·3389	0·3470	0·3305	0·3391	0·3378
C^t	0·1783	0·1875	0·1837	0·1918	0·1876	0·1882
$(\alpha\varepsilon_2)^t$	2·82	2·59	2·77	3·01	3·45	3·27
β^t	0·133	0·124	0·122	0·134	0·128	0·108
${}_{\infty}({}_{\mathrm{T}}P)^t$	104	103	108	114	125	121
${}_{\infty}({}_{\mathrm{T}}P)^{25}$	104	120	107	113	124	120

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA.

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63. *The Structure of Molecular Compounds. Part VII. Compounds formed by the Inert Gases.*

By H. M. Powell.

Preparation and some properties of the clathrate compound of argon and quinol are described. By crystallisation from water under 40 atmospheres' pressure of argon large and stable crystals containing nearly 9% by weight of argon are obtained. On heating they are converted into α-quinol with liberation of the argon. The volume of argon measured at room temperature and pressure is more than seventy times that of the crystals. Solution of the crystals liberates the gas. Other possible inert-gas compounds are discussed.

In the general series of molecular compounds of formula $3C_6H_4(OH)_2,M$, the component M may be argon. The first preparation of the *compound* was made by slow cooling of a solution of the components in benzene under 20 atm. pressure of argon (Powell and Guter, *Nature*, 1949, **164**, 240). The solvent was chosen as a result of previous experience in preparing the compound of quinol with carbon dioxide (Part IV, *J.*, 1948, 61), but the use of benzene results in a comparatively small yield owing to the low solubility of quinol in this solvent. The compound, being of the clathrate type, must be made from a solution containing dissolved molecules of the gas in sufficient concentration to cause the quinol molecules to separate out on cooling in the hydrogen-bonded cage form described as the β-quinol type of structure (Palin and Powell, Part VI, *J.*, 1948, 815). This form, different from the ordinary α-quinol, is produced in the presence of an appropriate concentration of a second component whose molecules are of suitable size to stabilise the cage structure in which they are enclosed.

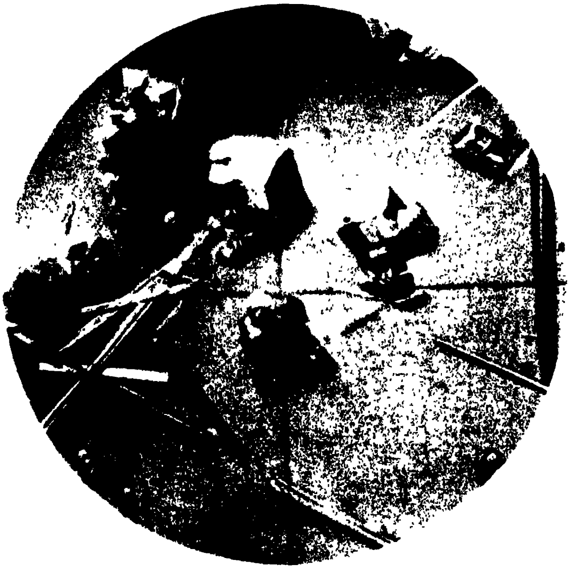
The present communication deals with new preparations and some properties of the products. The objects of these preparations were to obtain larger quantities of the material, to improve its purity, and to grow large single crystals for other investigations.

In order to obtain a greater concentration of quinol than is possible in a benzene solution, ethanol or water was used as solvent. Methanol was avoided since its molecules, in contrast with those of ethanol, are small enough to be enclosed to form the compound discussed in Part V (Palin and Powell, *J.*, 1948, 571). Water, which is used as solvent in the preparation of the quinol–sulphur dioxide compound, does not give a compound with quinol, but it was at first avoided since it had proved to be unsuitable in an attempted preparation of the carbon dioxide compound at a pressure of 50 atm. However, on trial with argon at somewhat lower pressure it has so far proved to be the best solvent.

The general method of preparation consists in making a solution of quinol saturated at room temperature, placing about 30 c.c. of this in a stainless-steel pressure vessel together with a further portion of quinol approximately equal in weight to the desired yield of compound, washing out atmospheric gases, and applying a pressure of argon from a cylinder, raising the temperature by heating the vessel in a large water-bath, and then allowing the solution to crystallise by slow cooling. The argon pressure is maintained by suitable additions from the cylinder.

The quantity of quinol taken should be such that it will dissolve when the temperature is raised. Usually much less was used than would have dissolved, and even so, considerable amounts of α-quinol sometimes came out with the compound. This is presumably due to a too rapid deposition of material with local impoverishment of the solution with respect to argon. The formation of the crystalline product takes place in the last stages of the cooling.

The need for a high pressure of argon is due to the low solubility of the gas. In the absence of any strong interaction between argon and quinol, the clathrate compound is formed by arranging for an argon atom to be available in position at the surface of the growing crystal whenever a cage of quinol molecules links up through its hydrogen bonds. The pressure is not required to prevent dissociation, since once the argon atom is enclosed it is retained by the strength of its cages, so that if sufficient time were allowed for the growth of the crystal it might form from a solution of very low argon concentration. For ordinary rates of crystallisation, obtained by allowing the water-bath to cool in the air, the pressure required to prevent local impoverishment of the solution might be expected to be of the same order of magnitude as that which the argon contained in the crystalline product would have if its cage surroundings were removed. From the known dimensions of the cages, which vary slightly but in a predictable way according to the dimensions of the enclosed molecule (Part VI), the volume of crystalline substance of formula $3C_6H_4(OH)_2,A$ which contains one g.-atom of argon is calculated to be approximately 260 c.c. This quantity of argon in the form of a gas



Photomicrograph of part of a mixed product. The large rhombohedra are crystals of the argon–quinol compound. The needles are α-quinol. Magnification × 40.

[*To face p.* 299.

occupying the same volume at 15° has a calculated pressure of 91 atmospheres. The present series of preparations has been made with argon at pressures up to 40 atmospheres. As is commonly the case with compounds of this type (Part VI), the quantity of argon is below that corresponding to the ideal formula owing to some cavities being left empty. The product of highest argon content so far obtained has the composition $3C_6H_4(OH)_2,0{\cdot}8A$, and therefore contains argon equivalent to a pressure of 73 atmospheres.

Observations on some prepared samples are given below. Argon contents were determined either from the weight of quinol recovered after liberation of argon by dissolution of the material in ether, or by heating the substance to 130°. For heating, the material is contained in a closed vessel to avoid loss of quinol which slowly sublimes. After the vessel has cooled, the liberated argon is displaced by air, and the weight of quinol residue determined. The nature of the crystalline samples was also examined in other ways. Crystals of the quinol–argon compound liberate large volumes of gas when covered with methanol which dissolves quinol, and, although α-quinol crystals sometimes give off a small amount of gas, there is no difficulty in distinguishing the two. With the aid of the microscope, or without it in the case of large crystals, the argon–quinol crystals may be recognised by their stumpy hexagonal prism form with terminal rhombohedral faces, or by their occurrence as rhombohedra of the type illustrated in the photomicrograph. Crystals of α-quinol were always very thin hexagonal needles, often striated lengthwise, and their terminal faces were usually indistinct. Differences in refractive indices could be used to distinguish the two materials but were not much employed since they are affected by the variation in composition of the compound. Single-crystal *X*-ray photographs give a sure proof of the presence of a component, and powder photographs were also employed for identification since a more representative sample of a mixed product is obtained by powdering a larger quantity. A preliminary trial showed that the compound is not affected by powdering. Differences of density make it possible to separate the constituents by flotation, but this procedure is not very effective since the densities vary on account of variable composition, occlusions in the crystals, and the tendency of the crystals to form aggregates.

EXPERIMENTAL.

(1) From 60 c.c. of benzene solution at 34 atm., 0·4 g. of product [Found: A, 4. Calc. for $3C_6H_4(OH)_2,A$: A, 10·8%] was obtained. The product contained needle-shaped α-quinol together with larger crystals of the argon compound in the form of rhombohedra. The difference is shown in the photomicrograph. As far as possible a mechanical separation was made. Both types of crystal are colourless and some of the argon-containing crystals are more needle-like than those shown in the photograph. This makes the separation difficult and the analysed portion is of uncertain purity.

(2) From 30 c.c. of ethanol solution at 40 atm., 5 g. of product (Found: A, 3·5%) were obtained. The crystals were of needle habit but usually of a more stumpy appearance than those of α-quinol, from which they may also be distinguished by their terminal rhombohedron faces when these are visible. The product contained some α-quinol.

A glass apparatus was constructed so that a known weight of the product could be placed in a bulb. A space above the crystals could be evacuated by means of a Hyvac pump and then isolated from the pump by a tap. The space, consisting of bulb and connecting tubes, was bounded by the surface of mercury in an attached manometer, and could be restored to a fixed volume by manipulation of the manometer until this mercury surface reached the fixed mark attained when the system was first evacuated. The volume of this space was determined by observing the temperature and pressure when a known mass of air was admitted from a second bulb, and, after the apparatus had been dismantled, was checked by the weight of water required to fill it, with allowance for the volume of crystals.

When the bulb containing a portion of the compound was heated slowly, the evolution of argon could be followed by observation of the manometer. The pressures observed were not equilibrium pressures and at any time the mercury level could be restored to its original position in order that the pressure might be read for a fixed volume of gas. After the evolution of gas at higher temperature, lowering of the temperature to a former value did not result in a decrease in pressure to the value previously observed at the lower temperature. At 40° gas was given off very slowly, the pressure being 1 mm. (compared with 762 mm. when all argon was liberated). At 70° a pressure of 29 mm. was observed, and this rose in the course of 5 minutes to 39 mm. Forty minutes later, after the temperature had been taken to 100°, the pressure recorded on restoring the temperature to 70° was 391 mm. The liberation of argon is very nearly complete at 130°, and at this temperature the solid has been converted into α-quinol. Raising the temperature until the quinol melts causes no appreciable change in the total amount of gas. The final pressure of the gas, at the fixed volume, was measured at room temperature, and, since the mass of gas liberated from the original weighed quantity of material was known, the density of the gas was calculated. The values observed, 0·0019 g./c.c., were usually slightly higher than the density of argon (0·0018 g./c.c. at N.T.P.). The argon used was spectroscopically pure, and the discrepancy is probably due to the argon content of the specimen being slightly over-estimated. The behaviour has not been fully investigated but it is known that a slight loss of wieght occurs slowly when certain samples of the argon compound are kept either in the atmosphere or in a desiccator. It may be due to the removal of small amounts of adhering solvent or to the escape of some argon. In either case this would mean that the true argon content of a sample from which the argon was released and measured would be less than that derived from an analysis carried out before the material was used, and thus would lead to a high value for the density.

(3) From 30 c.c. of aqueous solution at 40 atm., the argon–quinol compound was obtained in large single crystals in the form of hexagonal prisms with terminal rhombohedron faces. Some of these crystals were nearly 1 cm. long and several mm. in breadth. They were accompanied by crystals of α-quinol which always form as very thin needles. Separation of the two products could therefore be carried out by hand picking or by sieving, and the two parts examined separately. With other conditions kept as far as possible the same, the weight of product was varied by variation of the quantity of quinol used in the preparation. A yield of 6 g. was separated into nearly equal weights of α-quinol and the compound; one 3-g. yield contained at least 2·9 g. of the compound and very little α-quinol. However, the relative amounts of α-quinol and the compound obtained in different preparations in similar conditions were not constant, and it seems probable that the proportions are sensitive to conditions such as the frequency of formation of crystal nuclei which were not accurately controlled. However, the great ease of separation of the two constituents as formed from aqueous solution ensures an uncontaminated yield of the compound. The argon content in a typical sample was 8·8%, corresponding to 80% of the maximum possible argon content. An even greater proportion of occupied cavities may be expected with the more soluble heavier inert gases and the corresponding xenon compound should contain as much as 28% by weight of the inert gas.

Crystals of the argon compound have been preserved for weeks without visible change but some samples have been observed to lose weight, so far less than 1%. Some time will be necessary for the further examination of the keeping properties of the compound. Small quantities of solvent, which by successive attacks on different parts of the structure may detach quinol molecules, may cause the liberation of argon. It seems probable that in suitable conditions the compound would be a convenient portable source of argon, and the compounds of the heavier inert gases could be used similarly. The fact that the stable compound already prepared retains argon effectively at more than 70 atm. pressure is sufficient demonstration of the reality of the imprisoning action which is the basis of the concept of clathrate compounds. A fuller description of the relation of the argon atom to its surroundings is to be given with the crystal structure determination of the compound.

Some preliminary experiments were made concerning other possible compounds of similar type. All were carried out with 40 atm. pressure of inert gas, and in every case a preparation which had resulted in the formation of the argon compound was repeated with the substitution of another substance for quinol or for argon. The crystalline products were dissolved in suitable solvents and in no case was there any evolution of inert gas. Thus no compound was formed between argon and resorcinol, *p*-aminophenol, or *p*-phenylenediamine from ethanol solutions. Substitutes for quinol may be found among other substances capable of hydrogen-bond formation or in other classes of compound, but any exact prediction does not seem possible at present. No compound was formed between quinol and helium from benzene solution. The product was identified as α-quinol. This expected result may be explained by the small effective size of the helium atom, well known for its power of penetrating small spaces. The compound does not form because the helium atom cannot be retained by the quinol cages. A further attempt to prepare the helium–quinol compound in more favourable conditions is projected. It is not known whether neon will give a compound with quinol; it seems certain that the heavier inert gases will do so. Examination of these possibilities is intended.

The author thanks the Research and Development Department of the British Oxygen Company for their encouraging interest and for a supply of pure argon.

LABORATORY OF CHEMICAL CRYSTALLOGRAPHY
UNIVERSITY MUSEUM, OXFORD.

[*Received, September 20th,* 1949.]

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64. *The Structure of Molecular Compounds. Part VIII. The Compound of Krypton and Quinol.*

By H. M. POWELL.

By crystallisation of an aqueous solution of quinol under 20 atmospheres pressure of krypton the clathrate compound of composition $3C_6H_4(OH)_2,0{\cdot}74Kr$ [ideally $3C_6H_4(OH)_2,Kr$] is obtained in a form similar to that of the corresponding argon compound.

THE general series of clathrate compounds of ideal formula $3C_6H_4(OH)_2,M$ formed by quinol with a variety of substances M, which in their ordinary states at room temperature may be volatile liquids or gases, owe their existence to the formation by quinol, in the presence of the second component, of a special cage-like structure which imprisons single molecules M each in its own cavity. No ordinary chemical bonds are needed between quinol and the other molecule.

From the general properties and modes of formation it was suggested (Part IV, *J.*, 1948, 61) that the inert gases would form such compounds if a solution of quinol under high pressure of the inert gas were allowed to crystallise. The argon compound has already been prepared (Powell and Guter, *Nature*, 1949, **164**, 240; Powell, Part VII, preceding paper), but the helium compound appears not to exist. As discussed in Part IV, the enclosed molecule must satisfy certain requirements of size and shape. It must not be too large for the space available in the cavity although minor modifications in the shape of the enclosing quinol framework may be made to accommodate different molecules (Palin and Powell, Part VI, *J.*, 1948, 815). For a small effectively spherical molecule such as hydrogen chloride which does not completely fill the cavity, the two interpenetrating hydrogen-bonded quinol frameworks, which together form the walls of the enclosing cavities, adjust themselves to the equilibrium positions that they would occupy in the absence of any enclosed component, but for non-spherical molecules such as methyl cyanide the quinol structure distends in the manner of a piece of trellis. For enclosure of the inert-gas atoms the undistended form is to be expected and has been found for the argon compound. The absence of a helium compound is attributed to the small effective size of the atom, which could escape through a hole in the cage walls provided by six oxygen atoms linked through hydrogen bonds of length 2·75 A. along the sides of a plane hexagon. As shown in Part VI, a very slight distension of the quinol structure occurs when the methanol molecule is enclosed, and a molecule considerably larger than that of methanol, *e.g.*, methyl cyanide, will fit into the cavity by arranging its length in a way that fits the surrounding structure. The van der Waals radius for a CH_3 group in crystals is about 2 A., and it is therefore expected that spherical atoms of this size and somewhat larger will be enclosed and retained by the cages. From crystal-structure examinations the radii of the inert-gas atoms (for temperatures at which these substances solidify) are Ne 1·61, A 1·9, Kr 2·0, Xe 2·2 A. The radii for room temperature will be somewhat greater. The krypton atom, intermediate in size between argon and the methyl group, should therefore form a compound, and it seems probable that the xenon atom which is not much larger than a methyl group will be capable of enclosure in the same way. The solubilities in water of the inert gases increase with increasing atomic number, and since the higher solubility increases the chance of an inert-gas atom being available in the right place for enclosure, it may be expected that the compound will form more readily the higher the atomic number.

The krypton compound has now been prepared. 60 C.c. of a solution of quinol in water saturated at room temperature were contained in a pressure vessel with a further 2 g. of quinol. A pressure of 20 atm. of krypton was applied from a cylinder of the gas. The temperature was raised to 95° in order to dissolve the additional quinol, and the solution allowed to cool during 12 hours. The product consisted of crystals, some several mm. in thickness, similar in appearance to those of the argon compound, and distinguishable from a small amount of fine needles of α-quinol which also came out. A complete separation could not be made, and an analysed sample probably contained a small proportion of α-quinol. When heated to 120° with precautions to prevent loss of quinol by volatilisation, it lost 14·3% by weight. This corresponds to a composition $3C_6H_4(OH)_2,0{\cdot}67Kr$. As was expected, a somewhat higher krypton content was calculated from the density of a single selected crystal of the compound. This gave by flotation $d = 1{\cdot}51$ g./c.c., and for a unit cell of the same size as the argon compound this corresponds to 15·8% krypton content, *i.e.*, a composition $3C_6H_4(OH)_2,0{\cdot}74Kr$. Thus about three-quarters of the available cavities are occupied by krypton atoms. This may be compared with the 80% occupancy in the argon compound made in similar conditions but under 40 atmospheres' pressure. The procedure of the preparation excludes all possibility of anything but krypton being available for enclosure, and the high density cannot be explained except by the presence of these heavy atoms. Addition of methanol to the crystals causes dissolution with vigorous effervescence owing to liberation of krypton.

The author expresses his thanks to the British Oxygen Co., who provided a cylinder of krypton at the required pressure.

Laboratory of Chemical Crystallography,
University Museum, Oxford.

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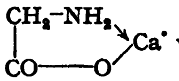
65. *The Extent of Dissociation of Salts in Water. Part XII. Calcium Salts of Some Amino-acids and Dipeptides.*

By C. W. Davies and (Mrs.) G. M. Waind.

The calcium ion has a marked tendency to associate with the anions of α-amino-acids in the following way: $Ca^{\cdot\cdot} + A' = CaA^{\cdot}$. The stabilities of a number of such association products of calcium with amino-acids and dipeptides are reported and discussed.

In a previous paper (*J.*, 1938, 277) it was shown that the aminoacetate anion, like the anions of α-hydroxy-acids, has a strong tendency to associate with the calcium ion in aqueous solution, and it was suggested that a chelate structure  $\begin{array}{l} CH_2{-}NH_2\searrow \\ |\qquad\qquad\quad Ca^{\bullet} \\ CO{-}{-}{-}O\nearrow \end{array}$ was possibly responsible for this. We have now extended this work to a number of other amino-acids and dipeptides at 25°, using the same method as before: the enhanced solubility of calcium iodate in a solution of the sodium salt of the amino-acid gives, after correction for interionic effects, a direct measure of the association of calcium with the added anion.

EXPERIMENTAL.

Materials.—Calcium iodate hexahydrate was prepared, and the solubility measurements were made, in the manner described previously (*J.*, 1938, 273, 277). Where only small amounts of saturating salt were available, as with the dipeptides and di-iodotyrosine, a smaller saturator was used, and the titrations were carried out on 10-ml. samples of the saturated solution.

The purity of the acids and dipeptides was checked by carrying out differential potentiometric titrations of their solutions against standard sodium hydroxide, using an "alki" electrode for pH's greater than 9, and applying the corrections of Jordan and Taylor (*J.*, 1946, 994). Stock solutions of the sodium salts were then made up in accordance with the observed end-points.

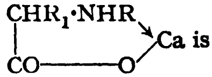
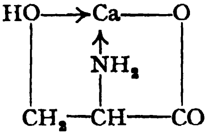
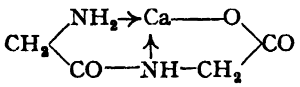
m.	*s.*	*K.*
Sodium aminoacetate.		
0	7·84	—
28·35	9·55	0·037
56·70	10·81	0·037
74·70	11·40	0·039
149·4	13·77	0·036
	Mean	0·037
Sodium α-aminopropionate.		
19·62	8·96	0·057
21·08	8·99	0·060
31·63	9·45	0·058
42·17	9·85	0·059
52·72	10·24	0·058
63·27	10·61	0·057
73·80	10·92	0·058
84·35	11·26	0·056
98·64	11·58	0·060
109·6	11·70	0·060
	Mean	0·058
Sodium salt of serine.		
11·22	8·62	0·034
21·10	9·20	0·036
56·10	10·68	0·040
	Mean	0·037
Sodium salt of glycylglycine.		
11·55	8·51	0·060
13·06	8·56	0·053
23·10	9·04	0·053
34·85	9·55	0·060
48·52	10·05	0·061
	Mean	0·057
Sodium salt of alanylglycine.		
61·22	9·83	0·22
Sodium salt of leucylglycine.		
52·55	9·61	0·20
Sodium salt of tyrosine.		
19·09	9·02	0·028
32·20	9·69	0·038
35·89	9·98	0·034
	Mean	0·033
Sodium salt of di-iodotyrosine.		
18·64	9·17	0·028
41·89	10·44	0·029
	Mean	0·029
Sodium hippurate.		
24·15	8·76	0·42
25·14	8·81	0·35
48·36	9·45	0·35
50·22	9·48	0·37
	Mean	0·37
Monosodium glutamate.		
22·22	8·87	0·071
23·00	9·06	0·060
44·50	9·86	0·065
46·47	9·92	0·067
90·26	11·05	0·068
92·85	11·14	0·068
	Mean	0·067
Disodium glutamate.		
5·62	8·68	0·0092
11·42	9·34	0·0096
21·43	10·42	0·0080
22·49	10·44	0·0083
	Mean	0·0088

Results.—These are given in the table. Col. 1 shows the concentration of the added salt, and col. 2 the measured solubility of calcium iodate hexahydrate, both in millimols. per litre. Col. 3 gives the calculated dissociation constant, $K = f_{Ca}f_{A}[Ca][A]/f_{CaA}[CaA]$, [A] being the concentration of the added anion. The calculations were made as in the earlier papers. The saturated solution contains $Ca^{\bullet\bullet}$, IO_3', $Na^{\bullet}$, A', and their possible association products, $CaIO_3^{\bullet}$, $NaIO_3$ and $CaA^{\bullet}$; NaA was assumed to be completely dissociated. The composition of the solutions was obtained by successive approximations from the known dissociation constants of $CaIO_3$, $K = 0{\cdot}13$, and of $NaIO_3$, $K = 3{\cdot}0$ and from the solubility product $\{Ca^{\bullet\bullet}\}\{IO_3'\}^2 = 7{\cdot}119 \times 10^{-7}$, using Davies's activity equation (*J.*, 1938, 2093). In the case of the disodium glutamate solutions, which are extensively hydrolysed, allowance had also to be made for the species OH', $CaOH^{\bullet}$, HG' and $CaHG^{\bullet}$ (G representing the doubly charged glutamate ion).

Discussion.

Greenwald (*J. Physical Chem.*, 1939, **43**, 379) has studied the association between magnesium and aminoacetate (glycine) ions, and has concluded that the formulation: $Mg^{\bullet\bullet} + 2G' \rightleftharpoons MgG_2$ fits the data better than does $Mg^{\bullet\bullet} + G' \rightleftharpoons MgG^{\bullet}$; this is contrary to the assumption we have used here and in the earlier paper quoted above. The data available to Greenwald were not very numerous or concordant, and our long series of solubility measurements with alanine was carried out to test the two possibilities more thoroughly. It will be seen that the *K* values derived for the $CaAl^{\bullet}$ ion leave little to be desired as regards constancy, and we conclude that up to a concentration of 0·1M. the tendency for association to go beyond the first stage is negligibly small. This agrees with what has been found previously for the association between the calcium ion and the anions of α-hydroxy-acids (*J.*, 1939, 279).

Of the eleven series of measurements reported in the Table, those involving the glutamic acid salts must be considered separately. The value $K = 0{\cdot}0088$ for calcium glutamate comes between the dissociation constants found by Topp and Davies (*J.*, 1940, 87) for calcium succinate (0·010) and calcium adipate (0·0064); there is no evidence that the amino-group exerts any influence in this case. In the monosodium glutamate solutions the anion is believed to be mainly $CO_2'\cdot CH_2\cdot CH_2\cdot CH(NH_3^{\cdot})\cdot CO_2'$, and this, in its association with the calcium ion, is not comparable with the other anions studied. In seeking for relationships between dissociation constant and structure, the data for tyrosine and di-iodotyrosine should also be excluded from the comparison. Both these compounds contain phenolic groups, and although the apparent constants reported in the table seem satisfactory, it is probable that neither is really a true constant for a single dissociation process, since the solutions studied will contain both $CO_2'{-}CH(NH_2){-}R{-}OH$ and $CO_2'{-}CH(NH_3^{\cdot}){-}R{-}O'$ (where R represents the remainder of the molecule).

The remaining seven constants all refer to univalent cations which will dissociate into $Ca^{\cdot\cdot}$ and ions of formula $NHR\cdot CHR_1\cdot CO_2'$. They cover a ten-fold range, from $K = 0{\cdot}037$ for the glycine salt, which is certainly abnormally weak, to $K = 0{\cdot}37$ for the hippurate, where the benzoylated amino-group would not be expected to exert any influence, and which is almost completely dissociated in dilute solution. So far as the figures go, they are consistent with the following two hypotheses: (*a*) that the tendency to form a chelate structure  $\begin{array}{l} CHR_1\cdot NHR \searrow \\ \vert \qquad\qquad\quad Ca \\ CO\text{———}O \nearrow \end{array}$ is rapidly reduced by weighting the glycine molecule with extraneous groups R or R_1; and (*b*) that the possibility of a tridentate configuration will enhance the tendency to associate with the calcium ion; this would account for the low constants found for serine and glycylglycine, where the structures  and  would be possible.

Edward Davies Chemical Laboratories,
Aberystwyth, Wales.

[*Received, October 4th*, 1949.]

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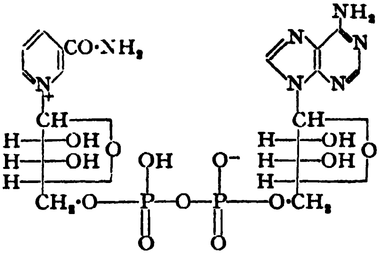
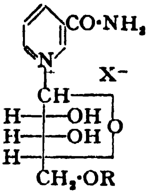
66. *Codehydrogenases. Part I. The Synthesis of Dihydronicotinamide-*D*-ribofuranoside* [N-D-*Ribofuranosidyl-*1 : 2(*or* 6)-*dihydronicotinamide*].

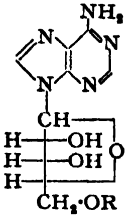
By L. J. Haynes and A. R. Todd.

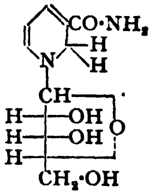
As a first step in a projected synthesis of cozymase, a number of *N*-glycosidyl-3-carbamylpyridinium bromides and their reduction products, the dihydronicotinamide glycosides, have been prepared, including a *dihydronicotinamide*-D-*ribofuranoside* [N-D-*ribofuranosidyl*-1 : 2(or 6)-*dihydronicotinamide*], probably identical with the dihydronicotinamide nucleoside prepared from natural cozymase. The formation of two (probably α- and β-) isomeric glucosides by condensation of α-acetobromoglucose with nicotinamide has been observed, and it is shown that quaternary glycosides can be formed from nicotinamide with both *cis*- and *trans*-acetobromosugars.

In recent years an extensive series of investigations has been undertaken in this laboratory, aimed at the clarification of structural problems in the nucleotide field by application of synthetic methods. One of these problems is the verification of the structures proposed for the so-called nucleotide coenzymes (adenosine di- and tri-phosphates, coenzymes I and II, and flavin-adenine-dinucleotide). Investigations leading to the synthesis of the natural purine and pyrimidine ribonucleosides and the development of methods of phosphorylation and polyphosphorylation have been described in papers published in this Journal (for summarised accounts see Todd, *J.*, 1946, 647; Lythgoe and Todd, *Symp. Soc. Exp. Biol.*, 1947, 1, 15; Todd, *Bull. Soc. chim.*, 1948, 933). On the basis of these studies it was possible to effect the total synthesis of the cophosphorylases adenosine diphosphate (Baddiley and Todd, *J.*, 1947, 648) and adenosine triphosphate (Baddiley, Michelson, and Todd, *Nature*, 1948, 161, 761; *J.*, 1949, 582). In continuation of our studies we have now devoted attention to the problem of a synthesis of cozymase (coenzyme I, codehydrogenase I, diphosphopyridine nucleotide), which acts as coenzyme in a number of biological oxidations. As a result of researches by von Euler, Schlenk, Warburg, and Karrer (for review see Lythgoe, *Ann. Reports*, 1945, **42**, 175) structure (I) has been advanced for cozymase mainly as a result of degradative work on this substance and the related coenzyme II (codehydrogenase II, triphosphopyridine nucleotide). Although the evidence for structure (I) seems conclusive, a total synthesis would be very desirable, not merely for purposes of confirmation, but also because it might make the substance more accessible in a pure condition and because it might be possible to apply the synthetic method to the production of a variety of structural analogues with which some study of the specificity of the coenzyme might be undertaken, or antagonists to it be discovered.


(I.)


(II.)


(III.)


(IV.)

The problem of a total cozymase synthesis in its most elementary form resolves itself into three parts: (1) the synthesis of "nicotinamide nucleoside" (II; R = H) and adenosine (III; R = H), (2) the phosphorylation of (II) and (III) to the corresponding nucleotides [II; R = $PO(OH)_2$] and [III; R = $PO(OH)_2$], and (3) the linkage of these nucleotides to yield cozymase. Of these various parts, adenosine (III; R = H) (Davoll, Lythgoe, and Todd, *J.*, 1948, 967; Kenner, Taylor, and Todd, *J.*, 1949, 1620) and adenosine-5′ phosphate [III; R = $PO(OH)_2$] (Baddiley and Todd, *loc. cit.*) have already been synthesised. The present communication deals with the synthesis of the dihydronicotinamide riboside (IV). In (IV) the formulation as a 1 : 2-dihydronicotinamide derivative is arbitrary; whether it is a 1 : 2- or 1 : 6-dihydro-compound is at present unknown (cf. Karrer, Schwarzenbach, Benz, and Solmssen, *Helv. Chim. Acta*, 1936, **19**, 811; Karrer, Schwarzenbach, and Utzinger, *ibid.*, 1937, **20**, 720).

The first recorded synthesis of a glycosidylpyridinium salt is due to Fischer and Raske (*Ber.*, 1910, **43**, 1750), who prepared *N*-2′ : 3′ : 4′ : 6′-tetra-acetyl D-glucosidylpyridinium bromide by allowing α-acetobromoglucose to react with pyridine in presence of phenol. In the course of the researches leading to the formulation of cozymase as (I) and the recognition that the active centre of the molecule in biological hydrogen transfer is the quaternary ammonium grouping (reversible reduction to a dihydro-compound), Karrer, Ringier, Büchi, Fritsche, and Solmssen (*Helv. Chim. Acta*, 1937, **20**, 55) extended the work of Fischer and Raske to the preparation of several related compounds. Acetobromoglucose, acetobromoarabinose, and acetobromoxylose were condensed with nicotinamide in dioxan solution and, in the case of acetobromoglucose, condensations were also carried out with other derivatives of nicotinic acid. In these experiments the preparation and purification of the pentose derivatives seem to have been troublesome, since analytical values are recorded only for the nicotinamide arabopyranoside. These quaternary salts showed oxidation–reduction properties similar to those of cozymase. That the nicotinamide–ribose linkage in cozymase was similar to that present in the synthetic materials was later shown by enzymic hydrolysis of the coenzyme with the nucleotidase obtained from sweet almond press-cake. This hydrolysis yielded adenosine and a "nicotinamide nucleoside" which, although devoid of coenzyme activity, showed properties analogous to those of Karrer's model substances. The "nicotinamide nucleoside" was an amorphous hygroscopic powder which retained moisture even when dried in a high vacuum (Schlenk, *Naturwiss.*, 1940, **28**, 46; *Svensk Akad. Kemi*, 1941, **14**, *A*, 13; *J. Biol. Chem.*, 1942, **140**, 619; *Arch. Biochem.*, 1943, **3**, 93; Schlenk and Gingrich, *J. Biol. Chem.*, 1942, **143**, 295; *J. Bact.*, 1944, **47**, 535).

We have further extended Fischer's synthesis to include the preparation of quaternary salts from nicotinamide and acetohalogeno-derivatives of D-mannopyranose, D-galactopyranose, and D-ribofuranose and have repeated the preparation of the D-glucose and L-arabinose derivatives already described by Karrer *et al.* (*loc. cit.*). The successful formation of a quaternary salt from α-acetobromo-D-mannopyranose calls for some comment. It has been stated by Micheel and Micheel (*Ber.*, 1930, **63**, 390; 1932, **65**, 253) that acetohalogeno-sugars, in which the halogen atom on $C_{(1)}$ is in the *trans*-position with respect to the acetyl groups at $C_{(2)}$ and $C_{(3)}$, will not react with tertiary bases to form quaternary salts, and that reaction with a tertiary amine to form a quaternary salt is diagnostic of a *cis*-acetohalogeno-sugar. α-Acetobromo-D-mannopyranose has, of course, a *trans*-configuration, and since it does form a quaternary salt with nicotinamide it is clear that the rule of Micheel and Micheel is not absolute. The German workers based their conclusions on experiments in which they attempted to cause acetobromomannose, acetochloromannose, and other acetohalogeno-sugars to react with trimethylamine in benzene, ethanol, or a mixture of these two solvents at room temperature or in sealed tubes at 100°. Examination of their results shows that, in experiments where no quaternary salt was formed, either starting materials were recovered unchanged (room-temperature experiments) or gross decomposition occurred (sealed-tube experiments at 100°).

In our early attempts to condense nicotinamide with α-acetobromo-D-mannopyranose (which we selected as a model compound in view of the configurational similarity of mannose and ribose), the two compounds were heated together under reflux for some hours in methyl cyanide solution. Although this procedure had given an excellent yield of quaternary salts with α-acetobromo-D-glucopyranose, no quaternary salt was formed, the main reaction being dehydrohalogenation of the sugar derivatives with formation of nicotinamide hydrobromide. Further experiments showed that, if the solution of the reactants was maintained at 40—50°, comparatively little nicotinamide hydrobromide was formed and *3-carbamyl-*N*-2′ : 3′ : 4′ : 6′-tetra-acetyl-*D*-mannopyranosidylpyridinium bromide* was produced in a yield of some 60%. A series of experiments on the general problem of the formation of quaternary salts from nicotinamide and acetohalogeno-sugars showed that acetofluoro-sugars are too unreactive to undergo either quaternary salt formation or dehydrohalogenation, while acetochloro-sugars (including α-acetochloro-D-glucopyranose) react more slowly than the corresponding bromo-compounds and undergo only the dehydrohalogenation reaction. Apparently quaternary salt formation and dehydrohalogenation are simultaneous competing reactions when acetobromo-sugars are used. Higher temperatures favour dehydrohalogenation, and in the case of the *trans*-acetobromo-sugars a difference of 30—40° in temperature may mean that the quaternary salt is formed almost exclusively or not at all. The " rule " of Micheel and Micheel has thus no general significance as a means of determining configuration in an acetohalogeno-sugar. Fischer and Raske (*loc. cit.*) reported that two forms of the quaternary acetylated glucoside were produced by condensation of pyridine with α-acetobromo-D-glucose. These two forms differed markedly in their physical properties, the first ($[\alpha]_D^{20} = -6{\cdot}43°$) being a crystalline compound, insoluble or sparingly soluble in organic solvents, and the second ($[\alpha]_D = +16{\cdot}2°$) an amorphous, very hygroscopic solid, easily soluble in methyl ethyl ketone but insoluble in ether. We have found that the condensation of nicotinamide with α-acetobromo-D-glucopyranose in methyl cyanide solution proceeds similarly; in addition to the crystalline compound ($[\alpha]_D^{19} = -18{\cdot}3°$) isolated by Karrer *et al.* (*loc. cit.*), it is possible to isolate an isomeric substance as a very hygroscopic amorphous solid, easily soluble in methyl cyanide, chloroform, and ethanol, and insoluble in ether ($[\alpha]_D^{19} = +20{\cdot}9°$). These two products are almost certainly α,β-isomers. With other acetobromo-sugars we obtained only amorphous glycosides and in no case were we able to obtain two distinct compounds; the possibility that some of these amorphous products may be mixtures of α- and β-forms cannot be excluded.

Reduction of the quaternary salts prepared from nicotinamide and acetobromo-D-glucopyranose, acetobromo-D-galactopyranose, acetobromo-D-mannopyranose, and acetobromo-L-arabopyranose with sodium dithionite yielded the corresponding acetylated dihydronicotinamide glycosides which could be readily reoxidised. It was found advantageous to carry out these reductions in an inert atmosphere and to avoid undue exposure of the products to light. The acetylated dihydro-glycosides were readily deacetylated with methanolic ammonia. With the exception of the glucose derivative already described by Karrer *et al.* (*loc. cit.*), all the compounds prepared were amorphous and hygroscopic and have so far defied all attempts at crystallisation; in the case of the quaternary salts, variation of the acid radical also failed to yield crystalline products. There can, however, be little doubt of their homogeneity, since repeated fractional precipitations gave products which showed no significant differences in physical or chemical characteristics. Mild acid hydrolysis of the quaternary acetylated galactoside gave *3-carbamyl-*N*-*D*-galactopyranosidylpyridinium bromide*, which was also amorphous.

Condensation of acetobromo-D-ribofuranose (Howard, Lythgoe, and Todd, *J.*, 1947, 1052) with nicotinamide gave a quaternary salt reduced by sodium dithionite to *dihydronicotinamide-*

(2′ : 3′ : 5′-*triacetyl* D-*ribofuranoside*) and from this product *dihydronicotinamide*-D-*ribofuranoside* [N-D-*ribofuranosido*-1 : 2(or 6)-*dihydronicotinamide*] (IV) was prepared as a pale yellow amorphous hygroscopic powder by deacetylation. It is not yet possible to say with certainty that this synthetic product is identical with Schlenk's dihydronicotinamide nucleoside, since the latter has been rather inadequately characterised, and in the absence of direct comparison the possibility that the natural and synthetic products might be α,β-isomers must be considered. The configuration of the natural product is, of course, unknown, although, since the natural purine and pyrimidine ribonucleosides have the β-configuration at the glycosidic carbon atom, one might well expect that the nicotinamide nucleoside would also be a β-compound. We incline to the view that the synthetic riboside we have obtained is, in fact, identical with the natural product on the following grounds. Schlenk and Gingrich (*loc. cit.*) have shown that nicotinamide nucleoside will replace coenzyme-I as a growth factor (V factor) for *Hæmophilus influenzæ* and *H. parainfluenzæ*, an effect not shown by nicotinamide or nicotinic acid. Tests carried out by Mr. D. A. Hughes of Sheffield University have shown that our synthetic dihydronicotinamide-ribofuranoside shows a similar effect, having an activity roughly half that of coenzyme-I on a molar basis.

EXPERIMENTAL.

(Analytical samples were dried *in vacuo* over phosphoric oxide at room temperature for several days. All evaporations under reduced pressure were effected at a bath temperature not exceeding 35°. Light petroleum refers to the fraction of b. p. 40—60°.)

Acetobromo-sugars.—Acetobromo-D-glucopyranose, -D-mannopyranose, -D-galactopyranose, and -L-arabopyranose were all prepared by the following method. The fully acetylated sugar was stirred with twice its weight of a solution of hydrogen bromide in glacial acetic acid (saturated at 0°) for a period of 2 hours, during which time the solid completely dissolved. Chloroform was then added, and the solution poured on ice, separated, and washed with ice-water until the washings were neutral to Congo-red. The chloroform solution was dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The residual syrup was taken up in dry ether, dry light petroleum added to faint cloudiness, and the solution set aside at 0° for some hours. The acetobromo-sugars crystallised in good yield and were sufficiently pure for further work if used within one or two days.

3-Carbamyl-2′-hydroxyethylpyridinium Bromide.—Ethylene bromohydrin (10 g., 1 mol.) and nicotinamide (10 g., 0·98 mol.) were refluxed in ethanol during 1 hour. The solvent was evaporated, and the residual gum caused to solidify by rubbing it with a few drops of ethanol. The *pyridinium bromide* (17·5 g., 87·5%) was thus obtained as a white crystalline powder, m. p. 141—144°. On recrystallisation from methanol by addition of ethyl acetate the m. p. rose to 148° (Found: C, 39·2; H, 4·5. $C_8H_{11}O_2N_2Br$ requires C, 38·9; H, 4·5%).

3-Carbamyl-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*glucopyranosidyl*)*pyridinium Bromide* (cf. Karrer *et al., loc. cit.*).—Acetobromo-D-glucopyranose (15 g.) and nicotinamide (5 g.) were gently refluxed in dry methyl cyanide (70 c.c.) during 3½ hours. A crystalline precipitate separated. The mixture was then set aside overnight and filtered. 3-Carbamyl-*N*-(2′ : 3′ : 4′ : 6′-tetra-acetyl (?β-)D-glucopyranosidyl)pyridinium bromide (13·78 g., 71%) was thus obtained as a white powder, which crystallised from methanol after the addition of ethyl acetate as colourless plates, m. p. 195—200° (decomp.) (Karrer *et al., loc. cit.*, give m. p. 192—200°, decomp.), $[\alpha]_D^{19}$ −18·3° (*c*, 2·5 in water). The filtrate was evaporated to dryness under reduced pressure; the residue, a dark oil, was taken up in chloroform (30 c.c.) and filtered, and anhydrous ether (150 c.c.) added. A white precipitate separated. This was washed well with ether and dried *in vacuo*. From its analysis and properties this material appeared to be an isomeric *3-carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* (?α-)D-*glucopyranosidyl*)*pyridinium bromide* (3 g., 15%) (Found: C, 45·3; H, 5·2. $C_{20}H_{25}O_{10}N_2Br$ requires C, 45·1; H, 4·7%), $[\alpha]_D^{19}$ = +20·9° (*c*, 2·5 in water).

N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* (?β-)D-*glucopyranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide* (cf. Karrer *et al., loc. cit.*).—A solution of sodium hydrogen carbonate (150 g.) in water (2½ l.) was saturated with carbon dioxide. The crystalline quaternary acetylated glucoside (20 g.) was then added. When this had completely dissolved, sodium dithionite (100 g.) was added. A brilliant yellow colour immediately appeared and there was a vigorous effervescence. The solution was set aside overnight in darkness, during which time a bulky precipitate of matted needles separated. On filtration and washing with water, *N*-(2′ : 3′ : 4′ : 6′-tetra-acetyl D-glucopyranosidyl)-1 : 2(or 6)-dihydronicotinamide (12·85 g., 75·5%) was obtained as a pale primrose-yellow solid, m. p. 155—157°, which after recrystallisation from water had m. p. 157° (Karrer *et al., loc. cit.*, give m. p. 157—158°), $[\alpha]_D^{18}$ = −11·1° (*c*, 0·8 in chloroform).

N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* (?α-)D-*glucopyranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide.*—The non-crystalline quaternary acetylated glucoside (1·85 g.), dissolved in an aqueous solution (200 c.c.) of sodium hydrogen carbonate (20 g.) which had been saturated with carbon dioxide, was treated with sodium dithionite (10 g.). A brilliant yellow colour immediately appeared and there was a vigorous effervescence. The solution was set aside overnight in darkness. No precipitate separated. The solution was extracted several times with chloroform, and the combined extracts washed with water and dried (Na_2SO_4). The chloroform solution was concentrated to small bulk under reduced pressure, and a large excess of dry light petroleum then added. A flocculent yellow precipitate formed. The bulk of the mother-liquor was decanted, and the residue dried *in vacuo*. N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* D-*glucopyranosidyl*)-1 : 2(or 6)-*dihydronicotinamide* (0·70 g., 46%) was thus obtained as a pale-yellow hygroscopic, amorphous powder, easily soluble in most organic solvents, but insoluble in light petroleum (Found: C, 49·9; H, 5·9; N, 5·7. $C_{20}H_{26}O_{10}N_2$ requires C, 52·8; H, 5·8; N, 6·2. $C_{20}H_{26}O_{10}N_2,1\frac{1}{2}H_2O$ requires C, 50·0; H, 6·0; N, 5·8%), $[\alpha]_D^{19}$ = +19·9° (*c*, 1·0 in chloroform).

3-Carbamyl-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*galactopyranosidyl*)*pyridinium Bromide.*—Acetobromo-D-galactopyranose (20 g., 1 mol.) and nicotinamide (6·0 g., 1·01 mols.), dissolved in methyl cyanide (100 g.), were kept at 60° during 6 hours and then at room temperature overnight. The solvent was then evaporated under reduced pressure. The residue, a light brown resin, was taken up in cold chloroform, set aside for some hours, and then filtered to remove separated nicotinamide hydrobromide (0·71 g.). The filtrate was evaporated to dryness under reduced pressure. 3-*Carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*galactopyranosidyl*)*pyridinium bromide* was thus obtained as a very hygroscopic " solid foam," soluble in chloroform, ethanol, and water, but insoluble in ether, ethyl acetate, and light petroleum; it could not be induced to crystallise. For purification, the quaternary salt was redissolved in dry chloroform, the solution filtered, and excess of dry ether added. A flocculent white precipitate formed. The mother-liquors were decanted, and the precipitate was washed 3 times by decantation with dry ether (Found: C, 44·2; H, 4·8; N, 5·2. $C_{20}H_{25}O_{10}N_2Br$ requires C, 45·1; H, 4·7; N, 5·3. $C_{20}H_{25}O_{10}N_2Br,\frac{1}{2}H_2O$ requires C, 44·4; H, 4·8; N, 5·2%), $[\alpha]_D^{18} = +15{\cdot}2°$ (*c*, 1·2 in water).

3-*Carbamyl*-N-D-*galactopyranosidylpyridinium Bromide*.—The quaternary acetylated galactoside (10 g.) was dissolved in water (25 c.c.) containing concentrated hydrobromic acid (0·5 c.c.), and the solution heated in a water-bath at 55—60° for 2 hours. The aqueous solution was evaporated to dryness under reduced pressure to give a colourless gum which was twice evaporated to dryness with ethanol under reduced pressure. The gum was dissolved in a small quantity of dry ethanol, and excess of anhydrous ether added. A precipitate formed which was coagulated by shaking overnight. The precipitate was filtered off and dried in a vacuum-desiccator. 3-*Carbamyl*-N-D-*galactopyranosidylpyridinium bromide* was thus obtained in good yield as a very hygroscopic amorphous powder, very soluble in water and ethanol, sparingly soluble in acetone, and insoluble in chloroform and ether. It retained solvent tenaciously (Found: C, 41·4; H, 5·5; N, 7·1. $C_{12}H_{17}O_6N_2Br,C_2H_5{\cdot}OH$ requires C, 41·0; H, 5·6; N, 6·9%).

N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* D-*galactopyranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide*.—The quaternary acetylated galactoside (15·9 g.) was dissolved in a saturated aqueous solution (600 c.c.) of sodium hydrogen carbonate which had been saturated with carbon dioxide. Sodium dithionite was added; a brilliant yellow colour immediately appeared and there was a vigorous effervescence. The solution was set aside overnight in darkness. No precipitate separated. The solution was 4 times extracted with chloroform, and the combined extracts washed with water and dried (Na_2SO_4). The chloroform solution was concentrated to small bulk under reduced pressure, and a large excess of dry light petroleum added. A slightly gummy yellow precipitate formed which broke up to a yellow powder on vigorous shaking of the mixture in a mechanical shaker. The mixture was set aside for 14 days, and the precipitate collected. N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* D-*galactopyranosidyl*)-1 : 2(or 6)-*dihydronicotinamide* (10·48 g., 77%) was obtained as a pale yellow, hygroscopic, amorphous powder, easily soluble in chloroform, ethanol, ethyl acetate, acetone, and methyl cyanide, sparingly soluble in ether and water, and insoluble in light petroleum and benzene. It could not be crystallised and became a glass at *ca.* 60° (Found: C, 53·3; H, 6·3; N, 5·9. $C_{20}H_{26}O_{10}N_2$ requires C, 52·8; H, 5·8; N, 6·2%), $[\alpha]_D^{18} = +10{\cdot}7°$ (*c*, 2·0 in chloroform).

3-*Carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*mannopyranosidyl*)*pyridinium Bromide*.—Acetobromo-D-mannopyranose (10 g., 1 mol.) and nicotinamide (3·4 g., 1·15 mols.) in methyl cyanide (60 c.c.) were kept at 60° for 7 hours and then at room temperature for 48 hours. The solution was then cooled to 0° and filtered from separated nicotinamide hydrobromide (0·85 g.). Evaporation of the fitrate to dryness under reduced pressure gave 3-*carbamyl*-N-(2′ : 3′ : 4′ : 6′-*tetra-acetyl* D-*mannopyranosidyl*)*pyridinium bromide* as a very hygroscopic uncrystallisable foam which was soluble in chloroform, alcohol, and water and insoluble in ether, ethyl acetate, and light petroleum. The material was purified as described for the galactose derivative (Found: C, 44·4; H, 4·8; N, 5·4. $C_{20}H_{25}O_{10}N_2Br$ requires C, 45·1; H, 4·7; N, 5·3. $C_{20}H_{25}O_{10}N_2Br,\frac{1}{2}H_2O$ requires C, 44·4; H, 4·8; N, 5·2%).

N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* D-*mannopyranosidyl*)-1 : 2(or 6)-*dihydronicotinamide*.—The quaternary acetylated mannoside (5·47 g.) was dissolved in a saturated aqueous solution (750 c.c.) of sodium hydrogen carbonate which had been saturated with carbon dioxide. Sodium dithionite (25 g.) was added, a brilliant yellow colour immediately developed and there was a brisk effervescence. The solution was set aside in darkness for 24 hours and then extracted with chloroform. The combined extracts were washed with water, and then dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. N-(2′ : 3′ : 4′ : 6′-*Tetra-acetyl* D-*mannopyranosidyl*)-1 : 2(or 6)-*dihydronicotinamide* (4·1 g., 88%) separated as a light-yellow hygroscopic solid which could not be crystallised (Found: C, 50·9; H, 5·9; N, 5·6. $C_{20}H_{26}O_{10}N_2$ requires C, 52·8; H, 5·8; N, 6·2. $C_{20}H_{26}O_{10}N_2,H_2O$ requires C, 50·9; H, 5·9; N, 5·9%).

3-*Carbamyl*-N-(2′ : 3′ : 4′-*triacetyl* L-*arabopyranosidyl*)*pyridinium Bromide*.—Acetobromo-L-arabopyranose (10 g., 1 mol.) and nicotinamide (3·6 g., 1·2 mols.) in methyl cyanide (60 c.c.) were kept at 80° during 5 hours and then overnight at 0°. Separated nicotinamide hydrobromide (1·36 g.) was filtered off, and the solvent evaporated from the filtrate under reduced pressure. The foam so obtained was purified by solution in chloroform and precipitation with ether as previously described. 3-*Carbamyl*-N-(2′ : 3′ : 4′-*triacetyl* L-*arabopyranosidyl*)*pyridinium bromide* was obtained as a hygroscopic amorphous powder, very soluble in chloroform, acetone, and water, but insoluble in ether, ethyl acetate, and light petroleum (Found: C, 43·3; H, 4·7; N, 6·0. $C_{17}H_{21}O_8N_2Br$ requires C, 44·3; H, 4·6; N, 6·1. $C_{17}H_{21}O_8N_2Br,\frac{1}{2}H_2O$ requires C, 43·4; H, 4·7; N, 6·0%).

N-(2′ : 3′ : 4′-*Triacetyl* L-*arabopyranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide*.—The quaternary acetylated arabinoside (1·25 g.) was reduced with sodium dithionite (5 g.) in sodium hydrogen carbonate solution (100 c.c.) by the procedure previously described. N-(2′ : 3′ : 4′-*Triacetyl* L-*arabopyranosidyl*)-1 : 2(or 6)-*dihydronicotinamide* (0·7 g., 66%) was obtained as a light-yellow hygroscopic solid, soluble in ethanol and chloroform, and insoluble in light petroleum; it could not be crystallised (Found: C, 50·7; H, 5·9; N, 6·9. $C_{17}H_{22}O_8N_2$ requires C, 53·5; H, 5·8; N, 7·3. $C_{17}H_{22}O_8N_2,H_2O$ requires C, 50·8; H, 6·0; N, 7·0%).

Dihydronicotinamide Glycosides [N-*Glycosido*-1 : 2(or 6)-*dihydronicotinamides*].—*General method* (cf. Karrer *et al.*, *loc. cit.*). The dihydro-acetylated *N*-glycoside was dissolved in methanol (dried by fractionation using a Fenske column), the solution cooled to 0°, saturated at 0° with anhydrous ammonia, and set aside for 24 hours at 0°. The solvent was evaporated under reduced pressure to leave a yellow solid residue. This was thoroughly extracted with ethyl acetate to remove acetamide, leaving the dihydro-glycoside as a pale yellow, hygroscopic, amorphous powder, which could not, except in the case of the glucoside described by Karrer, be crystallised, and was very readily oxidised when moist. In this way were obtained: *N*-D-glucosidyl-1 : 2(or 6)-dihydronicotinamide (93%), m. p. 199° (decomp.), after recrystallisation from water (Karrer *et al.*, *loc. cit.*, give m. p. 203—205°, decomp.), $[\alpha]_D^{18} = +4.9°$ (*c*, 1·5 in water); N-D-*galactopyranosidyl*-1 : 2(or 6)-*dihydronicotinamide* (96%) (Found: C, 48·9; H, 6·8; N, 9·8. $C_{12}H_{18}O_6N_2$ requires C, 50·3; H, 6·3; N, 9·8. $C_{12}H_{18}O_6N_2,\frac{1}{2}H_2O$ requires C, 48·9; H, 6·5; N, 9·5%), $[\alpha]_D^{18} = +36.5°$ (*c*, 2·5 in water); N-D-*mannopyranosidyl*-1 : 2(or 6)-*dihydronicotinamide* (*ca.* 80%) (Found: C, 48·6; H, 6·4; N, 9·0 $C_{12}H_{18}O_6N_2$ requires C, 50·3; H, 6·3; N, 9·8. $C_{12}H_{18}O_6N_2,\frac{1}{2}H_2O$ requires C, 48·9; H, 6·5; N, 9·5); and N-L-*arabopyranosidyl*-1 : 2(or 6)-*dihydronicotinamide* (*ca.* 80%) (Found: C, 50·3; H, 6·5; N, 10·2. $C_{11}H_{16}O_5N_2$ requires C, 51·6; H, 6·3; N, 11·0. $C_{11}H_{16}O_5N_2,\frac{1}{2}H_2O$ requires C, 50·0; H, 6·4; N, 10·6%).

N-(2′ : 3′ : 5′-*Triacetyl* D-*ribofuranosidyl*)-1 : 2(*or* 6)-*dihydronicotinamide*.—A solution of aceto-bromo-D-ribofuranose [from tetra-acetyl D-ribofuranose (2·35 g.) (Howard, Lythgoe, and Todd, *J.*, 1947, 1052] in dry methyl cyanide (15 c.c.) was cooled to 0° and added to a solution of nicotinamide (2 g.) in the same solvent (125 c.c.) at 0°. The solution was kept at 0° for 24 hours and then filtered from precipitated nicotinamide hydrobromide (1·0 g.). The filtrate was evaporated to dryness under reduced pressure at room temperature. The residue was dissolved in dry chloroform (15 c.c.), the solution filtered, and excess of anhydrous ether (80 c.c.) added. The precipitated white powder was washed by decantation 3 times with anhydrous ether. On drying *in vacuo* the crude quaternary glycoside (1·4 g.) was obtained as an extremely hygroscopic, amorphous powder. The quaternary salt (1·4 g.) was dissolved in a saturated aqueous solution (175 c.c.) of sodium hydrogen carbonate which had been saturated with carbon dioxide, and the aqueous solution was again saturated with carbon dioxide. Sodium dithionite (6 g.) was then added, a brilliant yellow colour immediately developed and there was a vigorous effervescence. The solution was set aside for 24 hours in darkness and extracted 6 times with chloroform. A nitrogen atmosphere was maintained wherever possible. The combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue, a solid foam, was purified by precipitation from chloroform solution with light petroleum. The N-2′ : 3′ : 5′-*triacetyl* D-*ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide* (0·45 g.) so obtained was a pale yellow, hygroscopic, amorphous solid (Found: C, 52·9; H, 5·9; N, 7·3. $C_{17}H_{22}O_8N_2$ requires C, 53·5; H, 5·8; N, 7·3%), $[\alpha]_D^{20} = -18.3°$ (*c*, 0·8 in chloroform).

N-D-*Ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide*.—The above acetylated glycoside (0·38 g.) was dissolved in anhydrous methanol (50 c.c.), and the solution cooled to 0°, saturated with anhydrous ammonia, and stored overnight at 0°. The solution was then concentrated under reduced pressure to small bulk, and excess of dry ethyl acetate (70 c.c.) added. The mixture was set aside for several days to age the precipitate, which was then washed thoroughly with dry ethyl acetate to remove acetamide. Filtration gave N-D-*ribofuranosidyl*-1 : 2(*or* 6)-*dihydronicotinamide* as a pale yellow amorphous powder, which could not be crystallised (Found: C, 48·3; H, 6·6; N, 9·7. $C_{11}H_{16}O_5N_2$ requires C, 51·6; H, 6·3; N, 10·9. $C_{11}H_{16}O_5N_2,H_2O$ requires C, 48·3; H, 6·6; N, 10·2%), $[\alpha]_D^{21} = -20.8°$ (*c*, 1·0 in water). The material was very soluble in water, and insoluble in ethyl acetate, light petroleum, ether, and chloroform; it was very hygroscopic and readily oxidised to a dark brown gum when moist.

We are indebted to Messrs. Imperial Chemical Industries Ltd. and Roche Products Ltd. for grants and gifts of material and to Mr. D. A. Hughes for microbiological assays. One of us (L. J. H.) participated in the investigation during his tenure of a D.S.I.R. Senior Research Award and an I.C.I. Fellowship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 6th,* 1949.]

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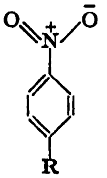
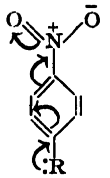
67. *The Magnetic Susceptibility of Certain Organic Compounds. Part III. The Contribution of the Nitro-group to the Magnetic Susceptibility of Aliphatic and Aromatic Nitro-compounds.*

By F. G. BADDAR and S. SUGDEN.

The magnetic susceptibility of certain aromatic and aliphatic nitro-compounds, as well as that of the corresponding parent substances, has been measured in an attempt to determine the contribution of the nitro-group to the magnetic susceptibility of these compounds. Col. 3 in Table III shows that the difference between the magnetic susceptibility of the $\rangle C-NO_2$ and the $\rangle C-H$ group is highest in the case of *m*-substituted nitro-compounds. This may be due to the fact that resonance leading to structures such as (III) is impossible in these *m*-compounds.

SEVERAL investigators have determined the magnetic susceptibility of the CH_2 group by measuring the susceptibility of a large number of the individuals of a homologous series, *e.g.*, aliphatic acids and their esters (French, *Trans. Faraday Soc.*, 1947, **43**, 356); alcohols, aliphatic acids, and their esters, and aromatic hydrocarbons (Angus and Hill, *ibid.*, 1943, **39**, 190); organic nitrites, nitrates, and nitro-compounds (Gray and Cruickshank, *ibid.*, 1935, **31**, 1491); normal alcohols (Cabrera and Fahlenbrach, *Z. Physik*, 1933, **85**, 568); and acetic acid and its esters (Woodbridge, *Physical Rev.*, 1935, **48**, 672). French (*Trans. Faraday Soc.*, 1945, **41**, 676) measured the susceptibility of certain disubstituted aromatic compounds. She noticed that, where the substituents are *op*-directing, the *o*-compounds have a markedly higher diamagnetic susceptibility value than either the *m*- or the *p*-isomerides. When the substituents are *m*-directing, the *m*-compounds have the highest susceptibility. She attributed this to the fact that in compounds containing two electron-repelling groups *ortho* to each other, there is the highest electron density, whereas in compounds containing two electron-attracting groups, the highest electron density is obtained when the two groups are *meta* to each other. However, she noticed that no such regularity could be traced in substituted aromatic nitro-compounds. It is possible that this irregularity may be due to the fact that in these compounds the contribution of the quinonoid structures (cf. III and IV) to the normal state of the molecule (*i.e.*, resonance) is affected by steric hindrance (cf. Birtles and Hampson, *J.*, 1937, 10; Ingham and Hampson, *J.*, 1939, 981) as well as by the position and polar nature of the substituents. Thus, in a molecule like p-R·C_6H_4·NO_2, the contribution of the quinonoid structures (III) or (IV) to the actual state of the molecule (or resonance hybrid) is higher if R is an electron-repelling group than if it is an electron-attracting group.


(I.)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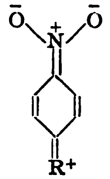
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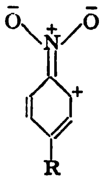
(IV.)

(R = H, CH_3, or NH_2.)

In the present investigation the magnetic susceptibility of certain aromatic and aliphatic nitro-compounds as well as of the corresponding parent substances was measured in an attempt to determine the contribution of the nitro-group to the magnetic susceptibility both in aliphatic and in aromatic compounds. To avoid inaccuracy due to unequal packing of solid substances, the measurements for such compounds were carried out in solution, using suitable solvents such as benzene, acetone, and ethyl acetate. The fact that the values of the magnetic susceptibility of the solid, deduced from that of its solutions in any two of these solvents at different concentrations, were found to be identical within the experimental errors, was considered to be a sufficient proof for the validity of the additivity law of solutions (see Table I).

In Table III, col. 3 represents the difference between the magnetic suceptibility of the $\rangle$C–NO_2 group and the $\rangle$C–H group. The unexpectedly low value ($-4\cdot45 \times 10^{-6}$) in the case of *p*-nitroaniline may be due to a solvent effect, whereas that in the case of nitromethane is more difficult to explain. It may be due to the uncertainty in the value of the magnetic susceptibility of methane, which is theoretically deduced (cf. Coulson, *Proc. Physical Soc.*, 1942, **54**, 51; French and Trew, *Trans. Faraday Soc.*, 1945, **41**, 439). It is noticed, however, that in the examples of aromatic nitro-compounds studied (*e.g.*, nitrotoluenes and nitroanilines) the differences in col. 3 of Table III are always highest in case of the *m*-, and lowest in the case of the *p*-derivatives. This may be due to the fact that structures such as (III) are impossible in the case of *m*-substituted nitro-compounds, and although it is possible in the case of the *o*-substituted compounds, yet it may be of less importance owing to steric hindrance (cf. Birtles and Hampson, *loc. cit.*). However, the contribution of the quinonoid structures such as (IV) increases in the case of nitro-compounds substituted by electron-repelling groups in the following order: Unsubstituted nitro-compounds < *m*-nitro- < *o*-nitro- < *p*-nitro-compounds, *i.e.*, nitrobenzene < *m*-nitrotoluene < *o*-nitrotoluene < *p*-nitrotoluene.

EXPERIMENTAL.

The measurements were carried out by the Gouy method using a silica tube which was calibrated by two nickel chloride solutions. Its volume was 25·18 c.c. and its constant (β) was 0·2824 (cf. Baddar, Hilal, and Sugden, *J.*, 1949, 132).

The solid materials used in these measurements were thoroughly purified by repeated crystallisation from pure solvents until a constant value for χ_s was obtained. Similarly, liquid substances were purified by repeated distillation from an all-glass apparatus, the middle fraction always being collected.

Purification of Materials.—Acetone and benzene were purified as stated by Baddar, Hilal, and Sugden (*loc. cit.*).

Ethyl acetate. "AnalaR" Reagent was washed with sodium hydrogen carbonate solution, then with water, and dried over calcium chloride for two weeks. It was fractionally distilled several times, and the fraction, b. p. 76·5—76·6°/756 mm., was collected; $d^{24\cdot95}$ 0·8941.

Toluene. Sulphur-free toluene was shaken with concentrated sulphuric acid, and washed with water, then with sodium carbonate solution to remove any sulphonated product. It was dried ($CaCl_2$), distilled, shaken several times with mercury, and repeatedly fractionated over sodium; b. p. 110·3—110·4°/768 mm.; $d^{24\cdot95}$ 0·8594.

Nitromethane. This was prepared according to *Org. Synth.*, Coll. Vol. I, p. 393; dried ($CaCl_2$), distilled, dried over phosphoric oxide for few hours, and fractionally distilled to give a colourless liquid, b. p. 100—100·4°/752 mm.; $d^{24\cdot95}$ 1·131.

2-*Nitropropane.* A sample kindly provided by I.C.I. Ltd. was washed with sodium carbonate solution, dried ($CaCl_2$), and distilled. The drying and distillation were repeated three times. It was finally kept over phosphoric oxide for two hours, decanted, and distilled in a vacuum to give a colourless liquid, b. p. 42°/40 mm., then redistilled at ordinary pressure, b. p. 119·8—120°/763 mm.; $d^{24\cdot95}$ 0·9828.

Tetranitromethane. Prepared according to Chattaway (*J.*, 1910, **97**, 2099) and purified by washing with sodium hydrogen carbonate solution (cf. Hammick *et al.*, *J.*, 1936, 1464), this was dried ($CaCl_2$) and distilled in vacuum, b. p. 58—59°/100 mm., then dried over phosphoric oxide for 2 hours, decanted, and distilled; b. p. 47·5—48·5°/40 mm. The product was frozen, and the liquid portion rejected, and the residue then twice distilled; b. p. 46°/36 mm.; $d^{24\cdot95}$ 1·6312.

Nitrobenzene and o- *and* m-*nitrotoluene.* A pure sample of each was washed with sodium carbonate solution, then with water, dried ($CaCl_2$), and distilled. It was twice frozen, the liquid portion being rejected, and dried (P_2O_5). By repeated fractional distillation the nitro-compounds were obtained as pale yellow liquids, b. p.s 207°/735 mm., 217—217·1°/738 mm., 228·5—229°/759 mm.; $d^{249\cdot5}$ 1·1974, 1·1580, and 1·1524, respectively.

Aniline. Aniline hydrochloride was crystallised from alcohol, and the pure salt treated with sodium hydroxide solution. The liberated aniline was extracted with ether, dried (KOH) for 3 days, and distilled in a carbon dioxide atmosphere to give a colourless liquid, b. p. 183—183·2°/759 mm. The drying and distillation were repeated several times, and the fraction of b. p. 183·4°/759 mm. was collected.

p-*Nitrotoluene.* This was melted under sodium carbonate solution, washed with water, dried, and crystallised from alcohol several times, to give colourless crystals, m. p. 54·5°.

o-, m-, *and* p-*Nitroaniline.* These were crystallised several times from dilute alcohol, m. p.s 71·6—71·8°, 114°, and 148·2°, respectively.

In all cases the measurement was repeated after redistilling or recrystallising the substance. A series of measurements (usually about 6) were then made with the exciting current alternately off and on and the mean reading was taken as the thrust on the specimen. From this was subtracted the thrust on the empty tube (−27·34 mg.), and then $\chi_s \times 10^6$ of the pure liquids was calculated from the formula of Nettleton and Sugden (*Proc. Roy. Soc.*, 1939, *A*, **173**, 313), *viz.*

$$10^6\chi_s = 0{\cdot}29v/w + \beta f/w$$

The meniscus correction, being negligibly small, was neglected.

For solids the magnetic susceptibility was obtained by preparing solutions of different concentrations of the solid substance in suitable solvents of known magnetic susceptibility. By measuring the susceptibility of the solution, and assuming that the additivity law holds for the constituents of the solution, the susceptibility of the solute can be calculated from the equation

$$10^6\chi_{\text{solution}} = 10^6\chi_{\text{solute}} \times x + 10^6\chi_{\text{solvent}}\,(1 - x),\ \text{where } x = \text{concn. of solute in g./g. of solution.}$$

By extrapolation to $x = 1$, the magnetic susceptibility of the solute was obtained.

The measurements were usually carried out in two different solvents, the mean value being taken in each case (see Table I).

To avoid the evaporation of the solvent during the transference of the solution to the specimen tube, the solution was prepared in a small wash-bottle with narrow delivery and pressure tubes closed by stoppers. After the solute and solvent had been weighed into the bottle it was kept in the balance case for ½ hour. The solution was then transferred to the specimen tube by applying a gentle stream of dry air saturated with the vapour of the solvent used.

In Table II sample (*b*) was obtained by redistillation of sample (*a*).

TABLE I.

Substance.	Solvent.	Concn. (x).	No. of detmns.	$-10\chi^6_{\text{sol.}}$	$-10^6\chi_s$.	$-10^6\chi_s$ (extrap.).	Mean.
o-Nitroaniline ……	Acetone	0·3362	5	0·5516	0·4943	0·4940	0·4954
,, ……	,,	0·3800	6	0·5477	0·4940		
,, ……	$CH_3{\cdot}CO_2Et$	0·3089	6	0·5795	0·4985	0·4967	
,,	,,	0·2424	6	0·5858	0·4939		
m-Nitroaniline …	Acetone	0·2156	5	0·5632	0·5000	0·4960	0·4985
,, …	,,	0·2960	5	0·5547	0·4933		
,, …	$CH_3{\cdot}CO_2Et$	0·1666	6	0·5966	0·5009	0·5009	
p-Nitroaniline …	Acetone	0·2046	5	0·5596	0·4769	0·4800	0·4842
,, …	,,	0·2374	5	0·5581	0·4848		
,, …	,,	0·2456	4	0·5552	0·4772		
,, …	,,	0·2594	6	0·5544	0·4798		
,, …	$CH_3{\cdot}CO_2Et$	0·1109	7	0·6016	0·4882	0·4882	
p-Nitrotoluene …	Acetone	0·3047	5	0·5632	0·5240	0·5253	0·5257
,, …	,,	0·3556	6	0·5615	0·5270		
,, …	Benzene	0·3096	6	0·6477	0·5261	0·5261	
,, …	,,	0·4112	7	0·6299	0·5263		

TABLE II.

Substance.	$-10^6\chi_s$. (*a*), mean of 6 readings.	$-10^6\chi_s$. (*b*), mean of 6 readings.	$-10^6\chi_s$, mean.	$-10^6\chi_M$.
Nitromethane	0·3452 ± 0·0004	0·3462 ± 0·0017	0·3457	21·10
2-Nitropropane	0·5131 ± 0·0004	0·5139 ± 0·0005	0·5135	45·73
Tetranitromethane	0·2195 ± 0·0003	—	0·2195	43·02
Nitrobenzene	0·5024 ± 0·0002	0·5026 ± 0·0003	0·5025	61·81
o-Nitrotoluene	0·5272 ± 0·0004	0·5271 ± 0·0009	0·5272	72·28
m-Nitrotoluene	0·5303 ± 0·0003	0·5305 ± 0·0004	0·5304	72·71
Toluene	0·7142 ± 0·0002	0·7157 ± 0·0010	0·7150	65·83
Aniline	0·6701 ± 0·0004	0·6704 ± 0·0006	0·6703	62·37
Ethyl acetate	0·6156 ± 0·0003	0·6155 ± 0·0003	0·6156	54·21

TABLE III.

Substance.	$-10^6\chi_M$.	$-\Delta 10^6\chi_M$, $\geqslant C{\cdot}NO_2 - \geqslant C{\cdot}H$.	Substance.	$-10^6\chi_M$.	$-\Delta 10^6\chi_M$, $\geqslant C{\cdot}NO_2 - \geqslant C{\cdot}H$.
Nitrobenzene	61·81 (1)	6·99	Nitromethane	21·10	5·1
Benzene	54·82		Methane	16·00	
o-Nitrotoluene	72·28 (2)	6·45	2-Nitropropane	45·37	6·37
Toluene	65·83		Propane	39·36	
m-Nitrotoluene	72·71 (3)	6·88	Tetranitromethane	43·02	6·75 $\left.\right\}$
Toluene	65·83 (4)		Methane	16·00	$\frac{(27\cdot02)}{4}$ $\left.\right\}$
p-Nitrotoluene	72·06 (5)	6·23			
Toluene	65·83				
o-Nitroaniline	68·42 (6)	6·05			
Aniline	62·37				
m-Nitroaniline	68·96 (7)	6·59			
Aniline	62·37				
p-Nitroaniline	66·82 (8)	4·45			
Aniline	62·37 (9)				

(1) Cf. Cabrera and Fahlenbrach, *Z. Physik*, 1934, **89**, 697; Bhatnagar and Mitra, *J. Indian Chem. Soc.*, 1936, **13**, 329; Bhatnagar *et al.*, *ibid.*, p. 273; *Z. Physik*, 1934, **89**, 506. (2) Cf. Bhatnagar, Mathur, and Mal, *Phil. Mag.*, 1930, **10**, 101; Cabrera and Fahlenbrach, *loc. cit.*; Bhatnagar and Mitra, *loc. cit.* (3) Cf. the first two references in (2). (4) Cf. Kido, *Sci. Rep. Tohoku Univ.*, 1936, **24**, 701; Boeker, *Physical Rev.*, 1933, **43**, 756; Angus and Hill, *loc. cit.* (5) Cf. Cabrera and Fahlenbrach, *loc. cit.*; Subramanian, *Proc. Indian Acad. Sci.*, 1936, **3**, *A*, 420; Bose, *Phil. Mag.*, 1936, **21**, 1119. (6) Cf. Bose, *loc. cit.* (7) Cf. Bose, *loc. cit.*; Krishnan and Banerjee, *Phil. Trans.*, 1935, **234**, *A*, 265. (8) Garssen, *Compt. rend.*, 1933, **196**, 541. (9) Cf. Oxley, *Phil. Trans.*, 1914, **214**, *A*, 109; Rao, *Indian J. Physics*, 1934, **8**, 483.

N.B.—(i) $-10^6\chi_M$ for *p*-nitrotoluene, *o*-, *m*-, and *p*-nitroaniline was determined by multiplying the values in the last column of Table I by the corresponding molecular weight.

(ii) The value for propane was derived from that of methane, the magnetic susceptibility increment for the two CH_2 groups being taken as 2 × 11·68 (cf. Angus and Hill, *loc. cit.*).

THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.

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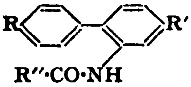
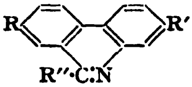
68. *Potential Trypanocides of the* N-*Heterocyclic Series. Part III. Alkoxy- and Hydroxy-phenanthridinium Salts.*

By F. C. COPP and L. P. WALLS.

The observation that a 9-phenylphenanthridinium salt with only methoxyl as substituent possessed significant trypanocidal properties suggested the examination of a series of such compounds and of similar compounds with hydroxyl groups. They were synthesised by conventional methods, and it has emerged that salts with an alkoxyl group in the 7-position are specifically active in *T. congolense* infections, and when in addition the 9-phenyl group has an amino- or a nitro-substituent the activity of some of these substances equals that of the diamino-salts previously described.

A LARGE number of amino-substituted phenanthridinium salts has been prepared (*J.*, 1945, 294; 1947, 67; 1948, 188) and it appeared that the presence of at least one amino-group in the diphenyl portion of the molecule was essential to trypanocidal activity (*Trypanosoma congolense*). This activity is much enhanced by the presence of a 9-phenyl group and of a second amino-group. Compounds which contain amino-groups substituted by acetyl, carbamyl, or carbalkoxy-groups are found to be much less active against *T. congolense*, although with the last-named modification some activity against the resistant trypanosome, *T. cruzi*, becomes apparent (Walls, Browning, Calver, and Leckie, *Nature*, 1946, **157**, 263; *J.*, 1946, 1031).


(I.)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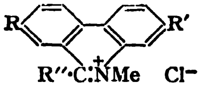
(III.)

Hitherto, the methoxy-group, which is known to exert a favourable therapeutic effect in other series, has not been introduced into the active phenanthridinium types, but its potential value was revealed when *7-methoxy-9-*p*-methoxyphenyl-10-methylphenanthridinium chloride* (III; R = OMe, R′ = H, R″ = p-OMe·C_6H_4) was found to possess significant trypanocidal activity. The effect of an association of alkoxy- and amino-groups and of hydroxy- and amino-groups was then examined, that type being selected in which the former group was located in the diphenyl portion of the molecule and the latter in the 9-phenyl group. Although compounds with amino-groups restricted to the 9-aryl group had hitherto shown practically no activity, the effect on them of the introduction of a 7-alkoxy-group is striking, many of the compounds now described being powerful trypanocides.

The alkoxy-compounds were prepared by the methods already used in this series, the essential step being the cyclisation of an appropriately substituted *o*-acylamidodiphenyl. *2-Amino-4′-methoxydiphenyl* and its higher homologues were prepared either from 4-amino-2′-acetamidodiphenyl (Petrow, *J.*, 1945, 119) or from 2-nitro-4′-hydroxydiphenyl. The latter substance had been previously prepared by Schultz, Schmidt, and Strasser (*Annalen*, 1881, **207**, 351) who gave only scanty preparative details. Our product had a much lower m. p. (114°) than that recorded by these authors (138°), but its structure was confirmed by its conversion into *2-acetamido-4′-methoxydiphenyl* (I; R = OMe, R′ = H, R″ = Me) and *2-acetamido-4′-(ethyl carbonato)diphenyl* (I; R = O·CO_2Et, R′ = H, R″ = Me), identical with the products obtained from 4-amino-2′-acetamidodiphenyl. *2-Nitro-4-methoxydiphenyl* was prepared from 3-nitro-4-aminoanisole and benzene by the Gomberg method, and reduced catalytically to *2-amino-4-methoxydiphenyl*. Condensation of these aminoalkoxydiphenyls with the appropriate acid chlorides yielded the amides (I), which were smoothly cyclised by phosphoryl chloride to the corresponding phenanthridines (II), the latter being readily converted into quaternary salts (III).

The various groups which were introduced into the 9-position are given in detail in the Experimental section (see Tables III, IV, and V); they include methyl, phenyl, phenyl substituted by nitro-, amino-, carbethoxyamino-, methoxy-, hydroxy-, or chloro-groups, and nitro- and amino-benzyl. The 9-aminophenyl compounds were prepared by cyclisation of 2-nitrobenzamidodiphenyls and subsequent reduction of the nitro-group. *2-*p*-Carbethoxyaminobenzamido-4′-methoxydiphenyl* (I; R = OMe, R′ = H, R″ = p-CO_2Et·NH·C_6H_4) was similarly cyclised to the *phenanthridine* (II; R = OMe, R′ = H, R″ = p-CO_2Et·NH·C_6H_4) but the corresponding quaternary *salt* could not be converted smoothly into the amino-salt, since the methoxy-group was also affected by the hydrolytic process used.

The preparation of the analogous 9-benzyl compounds (II and III; R = OMe, R′ = H, R″ = p-NO_2·C_6H_4·CH_2, etc.) presented no difficulty (cf. Part I, *J.*, 1948, 191). The rather low yield of 9-benzylphenanthridine reported by Ritchie (*Proc. Roy. Soc. N. S. Wales*, 1945, **78**, 150) may be attributed to the use of impure 2-phenylacetamidodiphenyl (m. p. 37°); our preparation of this compound (m. p. 85—86°) gave a 68% yield of the phenanthridine Our results therefore do not support his views on the cyclisation of the phenylacetamido-derivatives. *7-Methoxy-9-*p*-nitrobenzyl-10-methylphenanthridinium chloride* gave a deep-red product, presumably an anhydro-base, on treatment with water (see Part I).

The hydroxy-phenanthridines or -phenanthridinium salts (III; R or R′ = OH) were best prepared by demethylation of the appropriate methoxy-derivatives with concentrated hydrochloric acid at 160° (Woodruff and Conger, *J. Amer. Chem. Soc.*, 1938, **60**, 465). *7-Hydroxy-9-methylphenanthridine* (II; R = OH, R′ = H, R″ = Me) was thus obtained from the 7-methoxy-compound; it resulted also from the hydrolysis of *7-(ethyl carbonato)-* and *7-benzoyloxy-9-methylphenanthridine* (II; R′ = H, R″ = Me, R = O·CO_2Et and OBz, respectively), themselves the products of cyclisation of the corresponding *amides* (I; R′ = H, R″ = Me, R = O·CO_2Et and OBz, respectively) but in yields much lower than for the cyclisation of 2-acetamido-4′-methoxydiphenyl (I; R = OMe, R′ = H, R″ = Me). An attempt to obtain a hydroxyphenanthridine by diazotisation of 7-amino-9-*p*-nitrophenylphenanthridine led only to tars (cf. Part I).

The hydroxyphenanthridines could be alkylated to yield any desired ether, and this method was essential for the preparation of 7-*benzyloxy*-9-p-*nitrophenylphenanthridine*, since attempted ring-closure of 2-p-*nitrobenzamido*-4′-*benzyloxydiphenyl* led to debenzylation and the formation of an intractable resin.

Our colleagues, Dr. Brownlee and Mr. Goodwin, report that most of the quaternary salts prepared as above are powerfully antibacterial *in vitro* and one of them, 7-*methoxy*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride* (III; $R = OMe$, $R' = H$, $R'' = p\text{-}CO_2Et{\cdot}NH{\cdot}C_6H_4{\cdot}CH_2$), affords protection to mice against *Streptococcus pyogenes*. Certain of them (III; $R =$ alkoxyl, $R' = H$, $R'' = p\text{-}NO_2{\cdot}C_6H_4$ or *p*- or $m\text{-}NH_2{\cdot}C_6H_4$) possess a powerful curative action for *T. congolense* infections in mice, and consequently it can no longer be postulated that the presence of an amino-group in the diphenyl portion of the molecule is essential to high trypanocidal activity. It is of interest that the toxicity and activity of these salts are much influenced by the length of the *O*-alkyl group, the most active member being 7-*propoxy*-9-p-*aminophenyl*-10-*methylphenanthridinium chloride* (III; $R = OPr^n$, $R' = H$, $R'' = p\text{-}NH_2{\cdot}C_6H_4$). Although the 2-amino- were more active than the corresponding 7-amino-salts (Part I), the 2-methoxy- were much less active than the 7-methoxy-salts.

EXPERIMENTAL.

2-*Acetamido*-4′-*hydroxydiphenyl*.—4-Amino-2′-acetamidodiphenyl (42 g.) was dissolved in N-sulphuric acid (240 ml.) and diazotised with sodium nitrite (17 g.), more N-sulphuric acid (240 ml.) being added. The diazonium solution was decomposed under toluene. After 48 hours at 0°, the crude 2-*acetamido*-4′-*hydroxydiphenyl* that crystallised from the toluene was collected and dissolved in cold sodium hydroxide solution (charcoal). The filtrate was acidified and the solid thus precipitated crystallised from methanol, forming colourless needles (35 g.), m. p. 185—186° (Found: C, 74·05; H, 5·6. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8%).

2-*Acetamido*-4′-*methoxydiphenyl*.—A solution of 2-acetamido-4′-hydroxydiphenyl (61 g.) in N-sodium hydroxide (274 ml.) was heated on a steam-bath, and methyl sulphate (29 ml.) added gradually with stirring. After 1 hour the mixture was cooled, the resulting solid taken up into ether, and the ethereal solution washed with N-sodium hydroxide and dried. Evaporation of the ether left 2-*acetamido*-4′-*methoxydiphenyl*, b. p. 130°/0·01 mm. (50 g.). The colourless distillate crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in plates, m. p. 134° (Found: C, 75·1; H, 6·5. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%).

The following 2-acetamido-4′-alkoxydiphenyls were similarly prepared: 4′-*Ethoxy*-, b. p. 135°/0·01 mm., crystallised from aqueous *iso*propanol, m. p. 91° (Found: C, 75·1; H, 6·75. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7%). 4′-iso*Propoxy*-, crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 108—109·5° (Found: C, 75·9; H, 7·1. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 6·95%). 4′-n-*Butoxy*-, b. p. 155°/1 × 10^{-5} mm., crystallised from ether–light petroleum (b. p. 40—60°), m. p. 98° (Found: C, 76·6; H, 7·4; N, 4·8. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9%). 4′-*Benzyloxy*-, b. p. 190—200°/1 × 10^{-5} mm., crystallised from ethyl acetate, m. p. 138° (Found: C, 79·6; H, 5·8. $C_{21}H_{19}O_2N$ requires C, 79·5; H, 6·0%). 4′-(*Ethyl carbonato*)-, prepared from an alkaline solution of 2-acetamido-4′-hydroxydiphenyl and ethyl chloroformate, and crystallised from ethanol in colourless needles, m. p. 127—128° (Found: C, 68·2; H, 5·8. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7%). 4′-*Benzoyloxy*-, prepared by the Schotten–Baumann method, crystallised from methanol, m. p. 187—188° (Found: N, 4·4. $C_{21}H_{17}O_3N$ requires N, 4·2%).

2-*Nitro*-4′-*hydroxydiphenyl*.—A solution of 2-nitro-4′-aminodiphenyl (35·2 g.) in boiling N-sulphuric acid (640 ml.) was rapidly cooled to produce a fine paste, which was diazotised with sodium nitrite (9·5 g.). The diazonium solution was decomposed under toluene, which extracted the phenol as it was formed. After cooling, the toluene layer was extracted with aqueous sodium hydroxide, the phenol regenerated, and then crystallised from trichloroethylene as brownish crystals (22 g.), m. p. 110—112°, pure enough for the next stage. Its further purification was effected by percolating a benzene solution through a short column of alumina and extracting the filtrate with aqueous sodium hydroxide. The regenerated product now crystallised from trichloroethylene in lemon-coloured prisms, m. p. 114° (Found: C, 66·8; H, 4·3; N, 6·9. Calc. for $C_{12}H_9O_3N$: C, 67·0; H, 4·2; N, 6·5%).

From this product were prepared the *acetate*, m. p. 122° (Found: C, 65·6; H, 4·3. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%), *methyl ether*, m. p. 60—60·5° (Found: C, 68·0; H, 5·1; N, 6·1. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%), *ethyl ether*, m. p. 51° (Found: C, 69·2; H, 5·3. $C_{14}H_{13}O_3N$ requires C, 69·2; H, 5·4%), and *ethyl carbonate*, m. p. 121° (Found: C, 62·5; H, 4·4. $C_{15}H_{13}O_5N$ requires C, 62·4; H, 4·5%).

2-*Amino*-4′-*methoxydiphenyl*.—This was obtained in almost quantitative yield by catalytic reduction (5% palladium–charcoal) of 2-nitro-4′-methoxydiphenyl at 70° with hydrogen (50 atm.). The *amine* was an oil, b. p. 118—120°/0·1 mm., which, subsequently solidified, had m. p. 36° (Found: C, 78·4; H, 6·8. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%); its *hydrochloride* crystallised from 2N-hydrochloric acid in colourless needles, m. p. 227—228° (Found: C, 66·6; H, 6·4. $C_{13}H_{14}ONCl$ requires C, 66·4; H, 6·0%). Acetylation of the base with acetic anhydride gave 2-acetamido-4′-methoxydiphenyl identical with the product prepared from 4-amino-2′-acetamidodiphenyl as already described. By similar processes were prepared 2-*amino*-4′-*ethoxydiphenyl*, b. p. 130—135°/0·1 mm., m. p. 56° (Found: C, 79·1; H, 7·1; OEt, 20·9. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1; OEt, 21·1%), and 2-*amino*-4′-(*ethyl* *carbonato*)*diphenyl*, which crystallised from *cyclo*hexane in colourless prisms, m. p. 65—66° (Found: C, 70·3; H, 5·9. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%). Acetylation of the latter gave 2-acetamido-4'-(ethyl carbonato)diphenyl, identical with that previously described.

TABLE I.

o-*Acylamidodiphenyls* (I).

				Analysis.					
	Solvent for			Found, %.			Required, %.		
Diphenyls.	recrystn.	M. p.	Formula.	C.	H.	N.	C.	H.	N.
2-*Benzamido*-4'-*methoxy*-	Methanol	108°	$C_{20}H_{17}O_2N$	79·1	5·5	4·8	79·2	5·6	4·6
2-*Anisamido*-4'-*methoxy*-	Acetone	146	$C_{21}H_{19}O_3N$	76·0	5·7	—	75·6	5·9	—
2-p-*Chlorobenzamido*-4'-*methoxy*-	Ethanol	142—143	$C_{20}H_{16}O_2NCl$	(Cl, 10·0)		4·1	(Cl, 10·5)		4·1
2-p-*Nitrobenzamido*-4'-*methoxy*-	Ethanol	164—165	$C_{20}H_{16}O_4N_2$	69·0	4·55	8·3	69·0	4·6	8·1
2-m-*Nitrobenzamido*-4'-*methoxy*-	Ethanol	136·5—137	,,	69·1	4·8	8·4	,,	,,	,,
2-p-*Carbethoxyaminobenzamido*-4'-*methoxy*-	Methanol	178	$C_{23}H_{22}O_4N_2$	70·8	5·8	7·4	70·75	5·7	7·2
2-(3 : 5-*Dinitrobenzamido*)-4'-*methoxy*-	Acetic acid	179—180·5	$C_{20}H_{15}O_6N_3$	61·5	3·9	10·4	61·1	3·8	10·6
2-p-*Nitrobenzamido*-4'-*ethoxy*-	Ethanol	147	$C_{21}H_{18}O_4N_2$	—	—	7·9	—	—	7·7
2-p-*Nitrobenzamido*-4'-iso*propoxy*-	Ethanol	139	$C_{22}H_{20}O_4N_2$	69·9	5·2	7·5	70·2	5·4	7·4
2-p-*Nitrobenzamido*-4'-n-*butoxy*-	Ethanol	118	$C_{23}H_{22}O_4N_2$	—	—	7·2	—	—	7·2
2-p-*Nitrobenzamido*-4'-*benzyloxy*-	Ethyl acetate	146—147	$C_{26}H_{20}O_4N_2$	73·6	4·7	6·3	73·6	4·7	6·6
2-p-*Nitrobenzamido*-4'-*methoxy*-	Benzene	170	$C_{20}H_{16}O_4N_2$	—	—	8·0	—	—	8·1
2-*Phenylacetamido*-	*cyclo*Hexane	85—86	$C_{20}H_{17}ON$	83·2	6·1	5·1	83·6	5·95	4·9
2-p-*Methoxyphenylacetamido*-	*cyclo*Hexane	105	$C_{21}H_{19}O_2N$	79·7	6·2	4·7	79·5	6·0	4·4
2-p-*Nitrophenylacetamido*-4'-*methoxy*-	Benzene	149—150	$C_{21}H_{18}O_4N_2$	—	—	8·0	—	—	7·7

Alternatively, 2-acetamido-4'-methoxydiphenyl (50 g.) (prepared as previously described, from 4-amino-2'-acetamidodiphenyl) was dissolved in a mixture of concentrated sulphuric acid (24 ml.) and ethanol (450 ml.), and the mixture refluxed for 1½ hours. After neutralisation with ammonia the solution was evaporated under reduced pressure, the residue treated with excess of ammonia, and the precipitated oil extracted with ether. The ethereal solution was washed with water, dried, and evaporated; distillation of the residue gave 2-amino-4'-methoxydiphenyl (31 g.). By analogous processes were prepared: 2-amino-4'-ethoxydiphenyl, 2-*amino*-4'-iso*propoxydiphenyl*, b. p. 128—134°/0·05 mm. (Found: N, 6·3. $C_{15}H_{17}ON$ requires N, 6·2%), 2-*amino*-4'-n-*butoxydiphenyl*, b. p. 140°/0·003 mm. (Found: C, 79·6; H, 7·7; N, 6·1. $C_{16}H_{19}ON$ requires C, 79·65; H, 7·9; N, 5·8%), and 2-*amino*-4'-*benzyloxydiphenyl* which, crystallised directly from ethanol, had m. p. 122° (Found: N, 5·15. $C_{19}H_{17}ON$ requires N, 5·1%).

2-*Nitro*-4-*methoxydiphenyl*.—3-Nitro-4-aminoanisole (150 g.) (Fanter and Tarbell, *Org. Synth.*, **25**, 78) was dissolved in hot 10N-hydrochloric acid (280 ml.) with just enough water (75 ml.) to give a clear solution, which was cooled to 0° and diazotised with sodium nitrite (67·5 g.). It was then stirred vigorously with benzene (2 l.) at 5—10° and sodium acetate (300 g.) in concentrated aqueous solution added. After 48 hours the benzene layer was separated and washed with alkali, whereupon a thick tar separated; the benzene layer was decanted, washed with fresh alkali, and finally with water. The residue left after evaporation of the benzene was exhaustively extracted with boiling ether, the combined extracts were evaporated, and the residue was distilled in a vacuum. 2-*Nitro*-4-*methoxydiphenyl*, b. p. 120—135°/0·05 mm., subsequently solidified, and crystallised from carbon tetrachloride–light petroleum (b. p. 40—60°) as pale yellow needles, m. p. 75—77° (Found: C, 68·4; H, 4·5; N, 6·35. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%).

2-*Amino*-4-*methoxydiphenyl*.—A solution of 2-nitro-4-methoxydiphenyl in ethanol (250 ml.) was reduced over palladium-charcoal (4 g. of 5%) at 40—60° with hydrogen (50 atm.). The *amine* was an oil, b. p. 128—130°/0·08 mm. (Found: C, 78·4; H, 6·8; N, 7·2. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%).

p-*Carbethoxyaminobenzoic Acid*.—This acid has been described by Boehm and Mehta (*Ber.*, 1938, **71**, 1797) but their method has little preparative value. This acid is readily obtained by the action of ethyl chloroformate on an alcoholic solution of *p*-aminobenzoic acid in the presence of an equivalent of diethylaniline, or, alternatively, by the action of excess of this ester on an aqueous solution of the hydrochloride of *p*-aminobenzoic acid. The product crystallised from methanol in colourless needles,

Table II.

Phenanthridines (II).

Phenanthridines.	Solvent for recrystn.	M. p.	Yield, %.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
7-*Methoxy-9-methyl-*	Distilled, b. p. 141—148°/0·003 mm.	57°	60	$C_{15}H_{13}ON$	80·4	5·8	6·4	80·7	5·9	6·3
7-(*Ethyl carbonato*)-9-*methyl-*	*cyclo*Hexane	98—99	Variable	$C_{17}H_{15}O_3N$	72·6	5·5	—	72·6	5·4	—
7-(*Ethyl carbonato*)-9-*methyl-*, HCl	Ethanol	205—206	—	$C_{17}H_{16}O_3NCl$	64·4	5·4	—	64·2	5·1	—
7-*Benzoyloxy-9-methyl-*	Benzene	208—209	20	$C_{21}H_{15}O_2N$	80·7	4·75	4·5	80·5	4·8	4·5
7-*Methoxy-9-phenyl-*	Distilled, b. p. 190—192°/0·01 mm.	Gum	67	$C_{20}H_{15}ON$	—	—	4·7	—	—	4·9
7-*Methoxy-9-phenyl-*, *picrate*	Acetic acid	270—271	—	$C_{26}H_{18}O_8N_4$	—	—	10·75	—	—	10·9
7-*Methoxy-9-*p-*methoxyphenyl-*	Light petroleum (b. p. 80—100°)	94	80	$C_{21}H_{17}O_2N$	79·9	5·6	—	80·0	5·4	—
7-*Methoxy-9-*p-*chlorophenyl-*	Benzene and light petroleum (b. p. 80—100°)	157—158	73	$C_{20}H_{14}ONCl$	75·1	4·1	4·3	75·1	4·4	4·4
7-*Methoxy-9-*p-*nitrophenyl-*	Benzene	233—234	72	$C_{20}H_{14}O_3N_2$	72·6	4·3	8·4	72·7	4·3	8·5
7-*Methoxy-9-*m-*nitrophenyl-*	Benzene	183—184	81	,,	73·0	4·4	8·4	,,	,,	,,
7-*Methoxy-9-*p-*carbethoxyaminophenyl-*	Benzene	132—136	70	$C_{23}H_{20}O_3N_2,0{\cdot}5H_2O$	72·2	5·35	—	72·4	5·5	—
7-*Methoxy-9-*(3 : 5-*dinitrophenyl*)-	Pyridine	252—253	57	$C_{20}H_{13}O_5N_3$	—	—	11·1	—	—	11·2
7-*Ethoxy-9-*p-*nitrophenyl-*	Chloroform	233	60	$C_{21}H_{16}O_3N_2$	—	—	8·1	—	—	8·1
* 7-n-*Propoxy-9-*p-*nitrophenyl-*	Ethanol	169	60	$C_{22}H_{18}O_3N_2$	74·0	5·3	7·65	73·7	5·1	7·8
* 7-n-*Propoxy-9-*m-*nitrophenyl-*	Ethanol	146	60	,,	—	—	7·8	—	—	,,
7-iso*Propoxy-9-*p-*nitrophenyl-*	Ethanol	159—160	60	,,	74·1	5·2	7·9	73·7	5·1	,,
7-n-*Butoxy-9-*p-*nitrophenyl-*	Benzene	173	67	$C_{23}H_{20}O_3N_2$	—	—	7·6	—	—	7·5
* 7-*Benzyloxy-9-*p-*nitrophenyl-*	*n*-Propanol	180	70	$C_{26}H_{18}O_3N_2$	76·5	4·1	7·0	76·85	4·4	6·9
2-*Methoxy-9-*p-*nitrophenyl-*	Benzene	199	90	$C_{20}H_{14}O_3N_2$	—	—	8·3	—	—	8·5
9-Benzyl-	Ethanol	111—112	68	—	—	—	—	—	—	—
9-p-*Methoxybenzyl-*	Ethanol	125—127	70	$C_{21}H_{17}ON$	84·2	5·75	—	84·3	5·7	—
7-*Methoxy-9-*p-*nitrobenzyl-*	Toluene	142	93	$C_{21}H_{16}O_3N_2$	—	—	8·1	—	—	8·1
† 7-*Hydroxy-9-methyl-*	Nitrobenzene	298—300	95	$C_{14}H_{11}ON$	79·8	5·2	—	80·3	5·3	—
† 7-*Hydroxy-9-methyl-*, HCl	Water	285—287	—	$C_{14}H_{12}ONCl$	68·9	5·2	—	68·4	4·9	—
7-*Hydroxy-9-*p-*nitrophenyl-*	Acetic acid	275	80	$C_{19}H_{12}O_3N_2$	—	—	8·7	—	—	8·9
7-*Hydroxy-9-*m-*nitrophenyl-*	*iso*Propanol	250	75	,,	—	—	8·6	—	—	,,

* Prepared by alkylation of the appropriate 7-hydroxyphenanthridine.

† Prepared by alkaline hydrolysis of 7-(ethyl carbonato)-9-methylphenanthridine as well as by demethylation of 7-methoxy-9-methylphenanthridine.

m. p. 203° (Found: N, 6·9. Calc. for $C_{10}H_{11}O_4N$: N, 6·7%). It was converted into p-*carbethoxyaminobenzoyl chloride* by hot thionyl chloride; white needles, m. p. 110°, separated from benzene, (Found: N, 6·6; Cl, 15·6. $C_{10}H_{10}O_3NCl$ requires N, 6·15; Cl, 15·6%).

o-*Acylamidodiphenyls*.—The amides (Table I) were (with one exception) prepared by the following method. To a solution of the appropriate 2-amino-4′-alkoxydiphenyl (0·1 mole) in chloroform (200 ml.), anhydrous sodium carbonate (16 g.) was added, followed by the appropriate acid chloride (10% excess). The mixture was stirred for 30 minutes and then heated under reflux for a further 30 minutes. The hot solution was filtered, and the insoluble residue washed with warm chloroform. The combined filtrate and washings were evaporated to give the crude amide. *p*-Carbethoxyaminobenzoyl chloride and 2-amino-4′-methoxydiphenyl were condensed in boiling chlorobenzene.

TABLE III.

Alkoxy-10-*methylphenanthridinium salts* (III; R or R′ = alkoxyl).

(Chlorides, except where otherwise stated. All salts in this and succeeding tables were dried at 100° before analysis.)

				Analysis.			
	Solvent for			Found, %.		Required, %.	
Phenanthridinium salts.	crystn.	M. p.	Formula.	N.	Cl.	N.	Cl.
7-*Methoxy*-9-*methyl*- (*bromide*)	Water	238°	$C_{16}H_{16}ONBr$	(Br, 24·7)		(Br, 25·1)	
7-*Methoxy*-9-*phenyl*-	$Pr^{i}OH$ and Et_2O	216—217	$C_{21}H_{18}ONCl$	4·35	10·6	4·2	10·55
7-*Methoxy*-9-p-*methoxyphenyl*-	,,	215—216	$C_{22}H_{20}O_2NCl$	4·0	—	3·8	—
7-*Methoxy*-9-p-*chlorophenyl*-	Water	229—230	$C_{21}H_{17}ONCl_2$	,,	19·1	,,	19·2
7-*Methoxy*-9-p-*nitrophenyl*-	Dil. HCl	230—232	$C_{21}H_{17}O_3N_2Cl$	—	9·6	—	9·3
7-*Methoxy*-9-p-*aminophenyl*-	*iso*Propanol	253—254	$C_{21}H_{19}ON_2Cl$	—	10·3	—	10·1
7-*Methoxy*-9-p-*acetamidophenyl*-	Ethanol	258—259	$C_{23}H_{21}O_2N_2Cl$	7·3	—	7·1	—
7-*Methoxy*-9-p-*carbethoxy-aminophenyl*-	Ethanol	248—249	$C_{24}H_{23}O_3N_2Cl$	6·7	8·3	6·6	8·4
7-*Methoxy*-9-m-*nitrophenyl*-	Dil. HCl	229	$C_{21}H_{17}O_3N_2Cl$	7·3	—	7·4	—
7-*Methoxy*-9-m-*aminophenyl*-	Water	236—238	$C_{21}H_{19}ON_2Cl$	—	10·2	—	10·1
7-*Methoxy*-9-m-*carbethoxy-aminophenyl*-	EtOH and Et_2O	232—233	$C_{24}H_{23}O_3N_2Cl$	6·9	8·35	6·6	8·4
7-*Methoxy*-9-(3 : 5-*dinitro-phenyl*)-	Water	260	$C_{21}H_{16}O_5N_3Cl$	10·0	8·6	9·9	8·3
7-*Methoxy*-9-(3 : 5-*diamino-phenyl*)-	Ethanol	232—233	$C_{21}H_{20}ON_3Cl$	11·8	9·9	11·5	9·7
7-*Ethoxy*-9-p-*nitrophenyl*-	Dil. HCl	233	$C_{22}H_{19}O_3N_2Cl$	6·95	9·0	7·1	9·0
7-*Ethoxy*-9-p-*aminophenyl*-	Ethanol	225—226	$C_{22}H_{21}ON_2Cl$	7·6	9·6	7·7	9·7
7-n-*Propoxy*-9-p-*nitrophenyl*-	Dil. HCl	222	$C_{23}H_{21}O_3N_2Cl$	6·5	8·6	6·85	8·7
7-n-*Propoxy*-9-p-*aminophenyl*-	*iso*Propanol	215	$C_{23}H_{23}ON_2Cl$	—	9·5	—	9·4
7-n-*Propoxy*-9-m-*nitrophenyl*-	*iso*Propanol	212	$C_{23}H_{21}O_3N_2Cl$	—	8·4	—	8·7
7-n-*Propoxy*-9-m-*aminophenyl*-	Water	206	$C_{23}H_{23}ON_2Cl$	7·6	9·0	7·4	9·4
7-n-*Propoxy*-9-m-*carbethoxy-aminophenyl*-	*iso*Propanol	207	$C_{26}H_{27}O_3N_2Cl$	6·5	8·2	6·2	7·9
7-iso*Propoxy*-9-p-*nitrophenyl*-	Dil. HCl	239—240	$C_{23}H_{21}O_3N_2Cl$	6·8	8·9	6·85	8·7
7-iso*Propoxy*-9-p-*aminophenyl*- (*dihydrate*)	Water	174—175	$C_{23}H_{23}ON_2Cl$	7·4	9·6	7·4	9·4
7-n-*Butoxy*-9-p-*nitrophenyl*-	Water	234	$C_{24}H_{23}O_3N_2Cl$	6·7	8·8	6·6	8·4
7-n-*Butoxy*-9-p-*aminophenyl*-	*iso*Propanol	190	$C_{24}H_{25}ON_2Cl$	7·3	9·1	7·1	9·0
7-*Benzyloxy*-9-p-*nitrophenyl*-	Water	226	$C_{27}H_{21}O_3N_2Cl$	6·2	7·9	6·2	7·9
7-*Benzyloxy*-9-p-*aminophenyl*-	Dil. EtOH	184	$C_{27}H_{23}ON_2Cl$	6·2	8·3	6·6	8·3
2-*Methoxy*-9-p-*nitrophenyl*-	Methanol	234	$C_{21}H_{17}O_3N_2Cl$	7·2	9·1	7·4	9·3
2-*Methoxy*-9-p-*aminophenyl*-	Water	235	$C_{21}H_{19}ON_2Cl$	8·1	—	8·0	—

Phenanthridines and Phenanthridinium Salts.—These compounds (Tables II—V) were prepared by the following general methods. The *o*-acylamidodiphenyl was suspended in phosphoryl chloride (1 ml. to 1 g. of amide), and the mixture refluxed for 5 hours, and then decomposed with ice and water. The resulting solid was ground with a mixture of chloroform and concentrated hydrochloric acid, and the insoluble residue collected and washed with a little fresh chloroform and hydrochloric acid. Unchanged starting material was recovered from the chloroform solution. The chloroform-insoluble material, on being treated with aqueous ammonia, gave the almost pure phenanthridine. After recrystallisation from the appropriate solvent, the phenanthridine was treated with excess of methyl sulphate in nitrobenzene at 150° for 15 minutes. After cooling, the nitrobenzene was removed in steam, and the residual product extracted with hot water. The methochlorides were precipitated from the extract with concentrated hydrochloric acid. The aminophenanthridinium salts were prepared by reduction of the corresponding nitrophenanthridinium salts with a small excess of iron powder or a sludge of ferrous hydroxide. Demethylation of methoxyphenanthridines or methoxyphenanthridinium salts was effected by heating the starting material with excess of concentrated hydrochloric acid in a sealed tube at 160—170° for 3 hours. With cooling, the hydrochloride or chloride was collected, and the former basified to give the corresponding hydroxyphenanthridine.

Alkylation of Hydroxyphenanthridines.—The appropriate hydroxyphenanthridine was dissolved in an equivalent amount of sodium hydroxide solution and the solution stirred in an oil-bath at 120°

together with an excess (50%) of the appropriate alkyl iodide (or benzyl chloride). The reaction was slow and usually took about 12 hours for completion. The precipitated solid was collected, washed with water, and extracted with hot aqueous sodium hydroxide to remove unchanged starting material. The residue was then crystallised from the appropriate solvent.

TABLE IV.

Hydroxy-10-*methylphenanthridinium chlorides* (III; R or R′ = OH).

				Analysis.			
				Found, %.		Required, %.	
Phenanthridinium salts.	Solvent for crystn.	M. p. (decomp.).	Formula.	N.	Cl.	N.	Cl.
7-*Hydroxy*-9-*methyl*-	Methanol	262—263°	$C_{15}H_{14}ONCl$	5·4	13·6	5·4	13·6
7-*Hydroxy*-9-*phenyl*-	Water	263—264	$C_{20}H_{16}ONCl$	4·3	11·4	4·35	11·0
7-*Hydroxy*-9-p-*hydroxyphenyl*-	Aq. alcohol	264—265	$C_{20}H_{16}O_2NCl$	4·5	—	4·15	—
7-*Hydroxy*-9-p-*chlorophenyl*-	Dil. HCl	244—245	$C_{20}H_{15}ONCl_2$	4·0	20·0	3·9	19·9
7-*Hydroxy*-9-p-*nitrophenyl*-	Methanol	252	$C_{20}H_{15}O_3N_2Cl$	7·6	9·4	7·6	9·7
7-*Hydroxy*-9-p-*aminophenyl*-	Water	269—271	$C_{20}H_{17}ON_2Cl$	8·45	10·8	8·3	10·5
7-*Hydroxy*-9-p-*carbethoxy-aminophenyl*-	Methanol	281—282	$C_{23}H_{21}O_3N_2Cl$	7·1	—	6·7	—
7-*Hydroxy*-9-m-*aminophenyl*-	Water	275—277	$C_{20}H_{17}ON_2Cl$	8·6	10·4	8·3	10·5
7-*Hydroxy*-9-m-*carbethoxy-aminophenyl*-	Ethanol	198—200	$C_{23}H_{21}O_3N_2Cl$	(OEt, 11·5)	8·9	(OEt, 11·0)	8·7
2-*Hydroxy*-9-p-*nitrophneyl*-	Water	330	$C_{20}H_{15}O_3N_2Cl$	7·4	9·6	7·6	9·7
2-*Hydroxy*-9-p-*aminophenyl*-	Water	297—298	$C_{20}H_{17}ON_2Cl$	8·4	10·35	8·3	10·5

TABLE V.

9-*Benzyl*-10-*methylphenanthridinium chlorides* (III; R″ = benzyl).

				Analysis.			
				Found, %.		Required, %.	
Phenanthridinium salts.	Solvent for crystn.	M. p. (decomp.).	Formula.	N.	Cl.	N.	Cl.
9-*Benzyl*-	*iso*Propanol	205—207°	$C_{21}H_{18}NCl$	4·6	—	4·4	—
9-p-*Methoxybenzyl*-	*iso*Propanol	192	$C_{22}H_{20}ONCl$	—	9·8	—	10·1
7-*Methoxy*-9-p-*nitrobenzyl*-	Methanol	151	$C_{22}H_{19}O_3N_2Cl$	7·0	—	7·1	—
7-*Methoxy*-9-p-*aminobenzyl*-	Water	241	$C_{22}H_{21}ON_2Cl$	7·4	9·5	7·7	9·7
7-*Methoxy*-9-p-*carbethoxy-aminobenzyl*-	Ethanol	220	$C_{25}H_{25}O_3N_2Cl$	6·5	8·0	6·4	8·1
7-*Methoxy*-9-p-*propionamido-benzyl*-	Water	218	$C_{25}H_{25}O_2N_2Cl$	6·6	8·0	6·6	8·4
7-*Hydroxy*-9-p-*aminobenzyl*-	Water	252	$C_{21}H_{19}ON_2Cl$	7·8	10·0	8·0	10·1
7-*Hydroxy*-9-p-*carbethoxy-aminobenzyl*-	Dil. HCl	265	$C_{24}H_{23}O_3N_2Cl$	6·8	—	6·6	—

The phenanthridines are colourless or very pale yellow solids. The phenanthridinium salts are light yellow, except those with a 9-*p*-aminophenyl substituent which are bright red, and the 9-*m*-aminophenyl analogues which are very deep orange.

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CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT.

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69. *The Reactions of Propylene Sulphide with Acetyl Chloride and Related Compounds.*

By W. DAVIES and W. E. SAVIGE.

Acetyl chloride and propylene sulphide rapidly form 2-chloropropyl thiolacetate (II). Acetyl bromide behaves similarly, but acetic anhydride in the presence of pyridine gives 2-*acetylthiopropyl acetate* (X). These esters are converted into the corresponding mercaptopropanols, of which the structures have been proved by the properties of their crystalline derivatives. The two mercaptopropanols are converted by aqueous hydrochloric acid into the same chloropropanethiol [considered to be 2-chloropropane-1-thiol (IX)], which is also formed by the interaction of propylene sulphide and aqueous hydrochloric acid.

THE usual or " normal " interaction of compounds containing active hydrogen with asymmetrical ethylene oxides is to form derivatives of secondary alcohols, and the rare fission of asymmetrical ethylene oxides to form derivatives of primary alcohols is regarded as the abnormal process (Kadesch, *J. Amer. Chem. Soc.*, 1946, **68**, 41; Chitwood and Freure, *ibid.*, p. 680; Gilman and Fullhart, *ibid.*, 1949, **61**, 1478). This use of the terms " normal " and " abnormal " is adopted in the present paper with reference to the fission of ethylene sulphides to form secondary or primary thiols, respectively, or derivatives of them. Thus the conversion of propylene sulphide (I) into the derivative (X) of propane-2-thiol results from normal ring fission, as the sulphur atom retains its link with $C_{(2)}$.

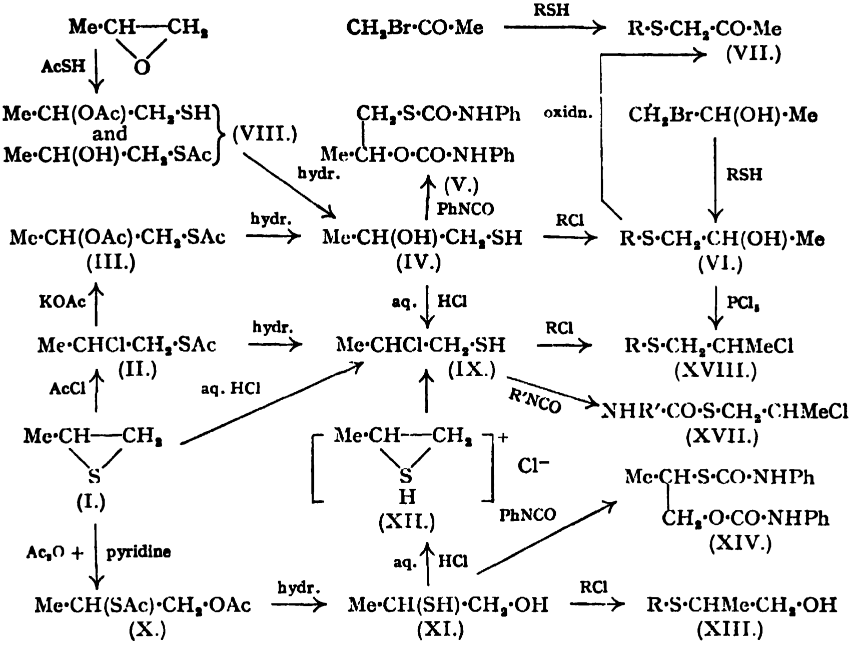
Propylene sulphide (I) reacts spontaneously with acetyl chloride to give 2-chloropropyl thiolacetate (II) in theoretical yield. This abnormal product shows no evidence of being a mixture of isomers. The compound (II) has already been described by Culvenor, Davies, and Heath (*J.*, 1949, 286), but its structure has not been proved. Its conversion into known crystalline derivatives is difficult, for it is inert to sodium iodide in boiling acetone, and is converted by zinc and acetic acid into viscous material; Raney nickel removes both sulphur and chlorine, and concentrated nitric acid gives an almost theoretical yield of sulphuric acid together with a small amount of oxalic acid. However, (II) is converted by potassium acetate in glacial acetic acid into 1-*acetylthio*-2-*propyl acetate* (III), which is hydrolysed by 1% methanolic hydrochloric acid to 1-mercaptopropan-2-ol (IV), a liquid characterised as the *derivative* (V) (obtained by interaction with 2 moles of phenyl *iso*cyanate) and as the 2 : 4 : 6-*trinitrophenyl thioether* (VI; R = picryl). The structure of (IV) is shown by its reaction with 1-chloro-2 : 4-dinitrobenzene and alkali to form 1-(2 : 4-*dinitrophenylthio*)*propan*-2-*ol* [VI; R = 2 : 4-$(NO_2)_2C_6H_3$], also obtained from 2 : 4-dinitrothiophenol and 1-bromopropan-2-ol and oxidised by chromic acid to (2 : 4-*dinitrophenylthio*) *acetone* (VII), which is identical with the reaction product from bromoacetone and 2 : 4-dinitrothiophenol.

This proof of the structure of (IV) is independent of previous work, and depends on evidence supplied by the properties of the 2 : 4-dinitrophenyl derivative. Sjöberg (*Ber.*, 1942, **75**, *B*, 27) found that propylene oxide and thiolacetic acid, $CH_3{\cdot}CO{\cdot}SH$, formed a mixture (VIII) of 1-acetylthiopropan-2-ol and 2-acetoxypropane-1-thiol, which gave (IV) on hydrolysis. These formulæ seem to have been assumed by Sjöberg by analogy with the products from glycidol and thiolacetic acid. A repetition of his work confirms his formula (IV), and thus proves that the reaction of propylene oxide with thiolacetic acid is a normal one.

Propylene sulphide reacts abnormally with acetyl bromide, and the apparently homogeneous 2-*bromopropyl thiolacetate* (over 95% yield) is converted into (III) by sodium acetate in glacial acetic acid. By analogy, the product from benzoyl chloride (Culvenor *et al.*, *loc. cit.*, pp. 284, 286) is 2-*chloropropyl thiolbenzoate*.

Alderman, Brubaker, and Hanford (U.S.P. 2,212,141) showed that ethylene sulphide reacts with acetic anhydride in the presence of a small quantity of pyridine to give the diacetate of 2-mercaptoethanol. They give, however, no details of the reaction with an asymmetrical sulphide, and it is now found that the main product (over 58% yield) from propylene sulphide is 2-*acetylthiopropyl acetate* (X). Possibly some (III) is also formed, although there is no evidence of its presence. The structure of (X) is proved by converting it into the corresponding 2-*mercaptopropan*-1-*ol* (XI), the boiling point of which is higher than that of the isomeric (IV). The 2 : 4-*dinitrophenyl thioether* [XIII; R = 2 : 4-$(NO_2)_2C_6H_3$] derived from (XI) has a much lower melting point than the isomer (VI). Though (XIII) is a primary alcohol, no carboxylic acid was isolated on oxidation with chromic acid, and potassium permanganate gives potassium 2 : 4-dinitrobenzene sulphonate. This permanganate oxidation, perhaps caused by the sulphur atom in (XIII) being attached to a secondary carbon atom, is again different from that of 2-(2 :4-dinitrophenylthio)ethan-1-ol, which gives the disulphone. Further, (XI) reacts with two moles of phenyl *iso*cyanate to form a *derivative* (XIV) different from (V). Hence, the structure of (XI) and the normal ring-opening of propylene sulphide by acetic anhydride in the presence of pyridine are definitely established.

Apparently, aqueous hydrochloric acid, like acetyl chloride and bromide, reacts abnormally with propylene sulphide, as a 50% yield of a liquid regarded as 2-chloropropane-1-thiol (IX) is isolated, and this is identical with the product obtained by hydrolysis of 2-chloropropyl thiolacetate (II). It is possible that the fission of propylene sulphide with hydrochloric acid leads to some of the normal isomer which then may give rise to some of the higher-boiling material obtained, just as the necessarily normal opening of ethylene sulphide with hydrochloric acid (Delépine and Eschenbrenner, *Bull. Soc. chim.*, 1923, **33**, 703) also yielded a high-boiling fraction. Samples of (IX), prepared by the four methods indicated in the diagram, seem to be identical, since there is no significant difference in their refractive index or boiling point, and they give identical *thiolurethanes* (XVII) with phenyl and α-naphthyl *iso*cyanate. On attempting to prepare the 2 : 4-dinitrophenyl thioether from (IX), the alkaline conditions required for the reaction result in the conversion of (IX) into propylene sulphide or a polymer (cf. the preparation of ethylene sulphides from 1 : 2-chloro-thiols, Coltof, U.S.P. 2,783,860), and no derivative is formed. However, (IX) obtained from (IV) or (XI) by hydrochloric acid, reacts with picryl chloride in the presence of sodium acetate to form the crystalline *thioether* (XVIII), which is also obtained from (VI) by phosphorus pentachloride. Because of the mild alkaline conditions employed, this production of (XVIII) from different samples of (IX) constitutes the best proof of their identity.


Me·CH—CH$_2$ / O
AcSH
Me·CH(OAc)·CH$_2$·SH and Me·CH(OH)·CH$_2$·SAc (VIII.)
CH$_2$Br·CO·Me
RSH
R·S·CH$_2$·CO·Me
(VII.)
oxidn.
CH$_2$·S·CO·NHPh / Me·CH·O·CO·NHPh (V.)
PhNCO
CH$_2$Br·CH(OH)·Me
RSH
hydr.
hydr.
Me·CH(OAc)·CH$_2$·SAc (III.)
Me·CH(OH)·CH$_2$·SH (IV.)
RCl
R·S·CH$_2$·CH(OH)·Me (VI.)
KOAc
aq. HCl
PCl$_5$
hydr.
Me·CHCl·CH$_2$·SAc (II.)
Me·CHCl·CH$_2$·SH (IX.)
RCl
R·S·CH$_2$·CHMeCl (XVIII.)
AcCl
aq. HCl
R′NCO
NHR′·CO·S·CH$_2$·CHMeCl (XVII.)
Me·CH—CH$_2$ / S (I.)
[Me·CH—CH$_2$ / S / H]$^+$ Cl$^-$ (XII.)
Me·CH·S·CO·NHPh / CH$_2$·O·CO·NHPh (XIV.)
PhNCO
Ac$_2$O + pyridine
aq. HCl
hydr.
RCl
Me·CH(SAc)·CH$_2$·OAc (X.)
Me·CH(SH)·CH$_2$·OH (XI.)
R·S·CHMe·CH$_2$·OH (XIII.)

R = 2 : 4-$(NO_2)_2C_6H_3$– or 2 : 4 : 6-$(NO_2)_3C_6H_2$–.
hydr. = hydrolysis by 1% methanolic hydrogen chloride.

The compound regarded as 2-chloropropane-1-thiol (IX) was first prepared by Sjöberg (*loc. cit.*) by the interaction of 1-mercaptopropan-2-ol (IV) and aqueous hydrochloric acid. However, this is no proof of structure, as the same compound is found to be similarly obtained from the isomeric 2-mercaptopropan-1-ol (XI). Apart from the fact that (IX) is obtained on hydrolysis of 2-chloropropyl 1-thiolacetate (II), the formula assigned to it is thought probable for the following reasons. Bennett and Hock (*J.*, 1925, **127**, 2671; Bennett, *Trans., Faraday Soc.*, 1941, **37**, 796) were the first to explain a number of fissions of carbon–sulphur links by means of an intermediary sulphonium ion. Ions of the type (XII) would be expected to be unstable, as it has been shown by Culvenor *et al.* (*loc. cit.*, p. 284) that the ring in aliphatic ethylene sulphides undergoes fission when the higher valency of sulphur is invoked. The rupture of (XII) to form a carbonium ion would, by analogy with the numerous nucleophilic attacks on the $C_{(2)}$ of propylene, be expected to produce (IX) rather than the unknown isomeric chloropropanethiol. This sulphonium ion concept explains the similar conversion (Fuson, Price, and Burness, *J. Org. Chem.*, 1946, **11**, 477), by hydrochloric acid, of both $R·S·CHMe·CH_2·OH$ and $R·S·CH_2·CHMe·OH$ into $R·S·CH_2·CHMeCl$ (where R = Et). A similar rearrangement involving nitrogen instead of sulphur is described by Schultz and Sprague (*J. Amer. Chem. Soc.*, 1948, **70**, 48).

The base-catalysed alcoholysis of propylene oxide (Chitwood and Freure, *loc. cit.*) is analogous to the normal opening of propylene sulphide with acetic anhydride containing pyridine, and can be attributed to the presence of pyridine acetate and to the acetate ion reacting with $C_{(1)}$ which has a lower electron density than $C_{(2)}$. The thiol group formed is then acetylated. It is noteworthy that this normal reaction is very much slower than the abnormal one with acetyl chloride.

The abnormal opening of the propylene sulphide ring by acetyl chloride and bromide, and probably by hydrochloric acid, affords interesting implications when compared with the action of such reagents on ethylene oxides. Propylene oxide and hydrochloric acid give the normal product almost entirely (Smith, *Z. physikal. Chem.*, 1919, **93**, 59), though acid-catalysed alcoholysis yields a mixture of normal and abnormal products (Chitwood and Freure, *loc. cit.*). There appears not to be a record of the action of acetyl halides on propylene oxide, but Sjöberg (*Chem. Abstr.*, 1943, **37**, 4363) shows that the product (73% yield) of the interaction of acetyl chloride and epichlorohydrin is normal, and that the product (37% yield) from glycidol is 92% normal. Similar results are obtained in the reaction of glycidol and epichlorohydrin with allyl alcohol in the presence of acid (Swern, Billen, and Knight, *J. Amer. Chem. Soc.*, 1949, **71**, 1152). The sulphur in ethylene sulphides is known to exert its higher valency towards methyl iodide far more easily than does the oxygen in ethylene oxides (Culvenor *et al.*, *loc. cit.*, p. 285) and it is tentatively suggested that hydrochloric acid and acetyl halides likewise form an onium ion to a greater extent with ethylene sulphides than with oxides. This would account for formation of much larger amounts of abnormal products from ethylene sulphides than from ethylene oxides.

Further work on a comparison of reactions of ethylene oxides and sulphides is being carried out. It is already clear that a deduction of the reactions of ethylene sulphides from formal analogy with those of ethylene oxides can be most misleading.

EXPERIMENTAL.

Reaction of Propylene Sulphide with Acetyl Halides.—Propylene sulphide was prepared from propylene oxide and thiourea by a modification of the method described by Culvenor, Davies, and Pausacker (*J.*, 1946, 1050). The preliminary stirring at 0° was omitted, the propylene sulphide added in portions, and the temperature maintained at 20° by efficient stirring and external temperature control during the whole reaction period of 3½ hours. Distillation of the product was effected without undue delay, fractionation giving a product, b. p. 74·5° (yield, 70%).

2-Chloropropyl thiolacetate (II) was prepared from propylene sulphide and acetyl chloride (Culvenor, Davies, and Heath, *J.*, 1949, 286). During fractionation, the b. p. (70—71°/9 mm.) and n_D^{15} (1·491) of the distillate remained constant. (II) was unchanged when boiled with dry pyridine in benzene, but was converted into high-boiling material by interaction with sodium cyanide in alcohol in the presence of a phenol buffer.

(II) (7·6 g.), anhydrous potassium acetate (7 g.), glacial acetic acid (5 ml.), and acetic anhydride (1 ml.) were refluxed until precipitation of potassium chloride ceased (3 hours). The cold mixture was agitated for a short time with water (30 ml.). The washed and dried ethereal extract gave 1-*acetylthio*-2-*propyl acetate* (III) (3·5 g.), b. p. 119—121°/19 mm., having a slight, pleasant odour (Found: C, 47·45; H, 7·05. $C_7H_{12}O_3S$ requires C, 47·7; H, 6·8%). The b. p. and n_D^{18} (1·467) were constant throughout the distillation.

1-Mercaptopropan-2-ol (IV) was obtained when (III) (3 g.) was heated under reflux with 1% methanolic hydrogen chloride (7 ml.) for 6 hours, the mixture being then distilled. (IV), b. p. 70—71°/20 mm., n_D^{16} 1·4815, is completely miscible with water, has an odour resembling that of mercaptoethanol, and gives colour tests characteristic of primary and secondary mercaptans (violet with aqueous sodium nitroprusside, and red with nascent nitrous acid). Sjöberg (*loc. cit.*) recorded b. p. 51°/12 mm. and n_D^{20} 1·4862 for the compound which he assumed to be 1-mercaptopropan-2-ol. (IV) and 2 moles of phenyl *iso*cyanate (cf. Bennett, *J.*, 1922, **121**, 2145) at 100° (2 hours) gave *propylene* 2-*phenylcarbamate* 1-*phenylthiolcarbamate* (V), m. p. 140·5°, prisms from alcohol–light petroleum (Found: N, 8·9. $C_{17}H_{18}O_3N_2S$ requires N, 8·5%). (IV) (0·1 g.) and picryl chloride (0·25 g.) were dissolved in alcohol (10 ml.), and a solution of anhydrous sodium acetate (0·1 g.) in alcohol (5 ml.) was added gradually with thorough mixing, a red colour being produced. After 5 minutes the mixture was warmed on the water-bath for 10 minutes. Addition of water gave 1-*picrylthiopropan*-2-*ol* (VI), m. p. 68°, lustrous light-yellow plates from aqueous alcohol (Found: N, 13·65. $C_9H_9O_7N_3S$ requires N, 13·85%). 1-(2 : 4-*Dinitrophenylthio*)*propan*-2-*ol* [VI; R = 2 : 4-$(NO_2)_2C_6H_3$], m. p. 94°, yellow warts from benzene–light petroleum (Found: N, 11·0. $C_9H_{10}O_5N_2S$ requires N, 10·85%), was obtained from equimolar proportions of (IV), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol (cf. Bennett and Whincop, *J.*, 1921, **119**, 1863). As shown by a mixed m. p., (VI) was also obtained from 1-bromopropan-2-ol, 2 : 4-dinitrothiophenol, and sodium hydroxide in alcohol, the reactants being warmed on the water-bath for 1 hour (cf. Willgerodt, *Ber.*, 1885, **18**, 328).

(2 : 4-*Dinitrophenylthio*)*acetone* [VII; R = 2 : 4-$(NO_2)_2C_6H_3$], m. p. 139°, pale yellow needles from aqueous dioxan (Found: N, 11·2; S, 12·85. $C_9H_8O_5N_2S$ requires N, 10·95; S, 12·5%), was obtained (*a*) when (VI) (0·5 g.) was dissolved in the minimum volume of glacial acetic acid, and a solution of sodium dichromate (0·7 g.) in dilute sulphuric acid (5 ml.) added gradually, the mixture being then boiled for 5 minutes, and (*b*) on warming equimolar quantities of bromoacetone, 2 : 4-dinitrothiophenol, and sodium hydroxide in alcohol for 10 minutes, as evinced by a mixed m. p. determination. (VII) is sparingly soluble in alcohol and its dioxan solution gives a red precipitate on treatment with a warm solution of *p*-nitrophenylhydrazine hydrochloride and does not decolourise cold dilute permanganate.

1-Mercaptopropan-2-ol (IV), prepared according to the method of Sjöberg (*loc. cit.*), had properties similar to those of a sample prepared by hydrolysis of (III) (*e.g.*, n_D^{16} 1·484, b. p. 50—55°/10 mm.). It reacted with 1-chloro-2 : 4-dinitrobenzene to give (VI), as evinced by a mixed m. p. determination.

2-*Bromopropyl thiolacetate* was obtained in 95% yield when propylene sulphide (14·8 g.) was added in small portions with slight agitation and external cooling to freshly distilled acetyl bromide (15·3 ml.), and the mixture was kept at 35° for 2½ hours before distillation (Found: S, 15·65. C_5H_9OSBr requires S, 16·25%). This liquid, b. p. 45°/0·2 mm. (85—88°/10 mm. with slight decomposition), n_D^{18} 1·521, if freshly distilled has the pleasant odour characteristic of thiol esters. However rapid decomposition occurs in air with development of the highly unpleasant odour of a halogeno-thiol and formation of hydrogen bromide. 2-Bromopropyl thiolacetate is stable in contact with aqueous sodium hydrogen carbonate. The pure liquid may be stored without decomposition in a sealed ampoule. Reduction of the ester with zinc dust and glacial acetic acid at 100° gave a halogen-free oil with an unpleasant odour, b. p. 96—104°/15 mm., n_D^{14} 1·458, which was apparently not the desired propyl thiolacetate as it is unchanged on attempted hydrolysis. Reduction of the ester with tin and hydrochloric acid caused rapid hydrolysis and subsequent polymerisation. Treatment with sodium acetate, using the method as described for the chloro-ester and potassium acetate, also yielded 1-acetylthio-2-propyl acetate (III), b. p. 112—114°/15 mm. (55% yield, the balance being polymer); its identity was established by hydrolysis with 1% methanolic hydrogen chloride to give 1-mercaptopropan-2-ol (IV), b. p. 58—60°/15 mm., identified by a mixed melting point determination of its 2 : 4-dinitrophenyl thioether (VI) which was obtained in 80% yield.

Reaction of Propylene Sulphide with Acetic Anhydride.—Propylene sulphide (14·8 g.), freshly distilled acetic anhydride (25 g.), and pyridine (1·5 ml.) were heated under reflux on the water-bath for 6 hours and then in an oil-bath at 130° for a further 3 hours. The product distilled over the range 97—103°/10 mm., further fractionation yielding *2-acetylthiopropyl acetate* (X), b. p. 103—105°/11 mm., n_D^{15} 1·4702 (20·6 g.) (Found: C, 47·5; H, 7·0. $C_7H_{12}O_3S$ requires C, 47·7; H, 6·8%). It has a slight, pleasant odour. Hydrolysis [method as for isomer (III)] yielded *2-mercaptopropan-1-ol* (XI), b. p. 60—62°/12 mm., 68°/25 mm., n_D^{17} 1·4818 (Found: C, 37·85; H, 8·6. C_3H_8OS requires C, 39·1; H, 8·7%). Like its isomer (IV), it is completely miscible with water, has a slightly unpleasant odour, and gives a mauve colour with sodium nitroprusside and a red colour with nitrous acid. During distillation of (X) and (XI) no change occurred. On heating (XI) at 100° for 2 hours with two moles of phenyl *iso*cyanate *propylene 1-phenylcarbamate 2-phenylthiolcarbamate* (XIV), m. p. 157·5°, prisms from aqueous alcohol (Found: N, 8·7. $C_{17}H_{18}O_3N_2S$ requires N, 8·5%), were obtained.

2-(2 : 4-*Dinitrophenylthio*)*propan*-1-*ol* [XIII; R = 2 : 4-$(NO_2)_2C_6H_3$], m. p. 64°, yellow warts from benzene–light petroleum (Found: C, 41·8; H, 3·7. $C_9H_{10}O_5N_2S$ requires C, 41·85; H, 3·85%), was obtained from (XI), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol [method as for (VI), crystallisation being difficult]. Oxidation of (XIII) with chromic acid gave a polymer and water-soluble material which is difficult to extract. Oxidation at 70° with 3% aqueous potassium permanganate gave potassium 2 : 4-dinitrobenzenesulphonate (Found: N, 10·15. Calc. for $C_6H_3O_7N_2SK$: N, 9·8%), which explodes on heating and is soluble in water. 1-(2 : 4-Dinitrophenylthio)propan-2-ol, prepared by the method of Bennett and Whincop (*loc. cit.*) from mercaptoethanol, 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol, when similarly oxidised with potassium permanganate yielded white plates, m. p. 183—185°, on extraction with ether. The m. p. was not depressed on admixture with an authentic specimen of 2 : 4-dinitrophenylsulphonylmethane.

Reaction of Propylene Sulphide with Hydrochloric Acid.— A solution of propylene sulphide (14·8 g.) in methanol (20 ml.) was added with shaking and external cooling to a solution of concentrated aqueous hydrochloric acid (25 ml.) in methanol (30 ml.), and the mixture set aside for 19 hours, after which an unpleasant-smelling oil separated. Water (100 ml.) was added and the oil extracted with chloroform without delay, washed, dried ($CaCl_2$), and distilled. A small amount of propylene sulphide distilled and then a fraction, b. p. 59—61°/80 mm. Redistillation gave 2-chloropropane-1-thiol (IX), b. p. 124—125°/760 mm., 60°/80 mm.; n_D^{13} (1·484) of the distillate did not vary during the distillations, even when a fractionating column was used. The yield was 11·0 g., higher-boiling halogen-containing liquids comprising the balance. Sjöberg (*loc. cit.*) records b. p. 125—125·5°/764 mm., n_D^{20} 1·4852 for the compound which he assumes to be 2-chloropropane-1-thiol, and reports it to be decomposed immediately by aqueous alkali. Though (IX) does not form a derivative with 1-chloro-2 : 4-dinitrobenzene and sodium hydroxide, or with 1-fluoro-2 : 4-dinitrobenzene and sodium acetate, the unpleasant odour of the halogeno-thiol is replaced by the rather fragrant odour of propylene sulphide, and sodium chloride is precipitated. (IX) is comparatively inert to phenyl *iso*cyanate, heating in a sealed tube at 160° for 3 hours being necessary to effect conversion into *2-chloropropyl 1-phenylcarbamate* (XVII), m. p. 91·5°, prisms from light petroleum containing a few drops of benzene (Found: N, 6·3; S, 14·35. $C_{10}H_{12}ONSCl$ requires N, 6·1; S, 13·95%); this derivative is obtained in good yield from both first and last fractions of the distillate. Similarly (IX) reacts with α-naphthyl *iso*cyanate to give *2-chloropropyl 1-α-naphthylthiolcarbamate*, m. p. 110° (Found: N, 5·0. $C_{14}H_{14}ONSCl$ requires N, 5·0%). 2-Chloropropane-1-thiol (IX) was again obtained when 2-chloropropyl thiolacetate (II) (7·6 g.) was heated under reflux for 2 hours with 2% methanolic hydrogen chloride. Distillation gave 3·4 g. of product, b. p. 67—68°/85 mm., 124—125°/760 mm., n_D^{14} 1·484, which yielded with phenyl and α-naphthyl *iso*cyanates, respectively, the derivatives reported above. The residue from the distillation was a mobile, halogen-containing liquid of very high b. p. Distillation of a crude sample of (IX) at atmospheric pressure resulted in profound decomposition and the product contained hydrogen chloride and a liquid (b. p. 77°) with the odour of propylene sulphide; this, on storage, was replaced by that of the chloro-thiol.

2-Chloropropane-1-thiol (IX), prepared according to Sjöberg (*loc. cit.*) by treatment of 1-mercaptopropan-2-ol (IV) with concentrated aqueous hydrochloric acid, had b. p. 58—60°/80 mm., 124—125°/760 mm., n_D^{16} 1·486, and n_D^{14} 1·487. The yield was 66%, the residue consisting of high-boiling halogen-containing liquid. (IX) prepared by this method also gives derivatives with phenyl and α-naphthyl *iso*cyanates identical with those from (IX) prepared from propylene sulphide and hydrogen chloride. Also, (IX) (0·15 g.), picryl chloride (0·24 g.), and anhydrous sodium acetate (0·2 g.) in alcohol (5 ml.), on storage for 16 hours and dilution with water, yielded *2-chloro-1-picrylthiopropane* (XVIII; R = picryl), m. p. 86°, small yellow needles from benzene–light petroleum (Found: N, 12·85. $C_9H_8O_6N_3SCl$ requires N, 13·05%). (XVIII), which contained halogen, gave an appreciable depression in m. p. on admixture with picryl chloride, but not with the product obtained on treatment of (VI) in chloroform with phosphorus pentachloride, followed by evaporation of the solvent and pouring of the mixture into water.

2-Mercaptopropan-1-ol (XI) (4·2 g.) and concentrated aqueous hydrochloric acid (17 ml.) were warmed on the water-bath. An immediate turbidity developed, and after 15 minutes the mixture was cooled and the oily layer extracted with ether, dried ($CaCl_2$), and distilled. The distillate, b. p. 41°/30 mm., 55°/50 mm., 62°/70 mm., n_D^{14} 1·488, gave steady boiling points when distilled at different pressures. With phenyl *iso*cyanate and picryl chloride respectively it gave derivatives identical with those obtained from (IX) prepared by the interaction of (IV) and hydrogen chloride.

The micro-analyses were made by N. L. Lottkowitz and N. W. Gamble. One of us (W. E. S.) acknowledges financial assistance from the Commonwealth Reconstruction Training Scheme.

Organic Chemistry Laboratory,
University of Melbourne.

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70. *Experiments on the Synthesis of Carbonyl Compounds. Part I. Introduction. The Acidolysis of Acylmalonic Esters.*

By R. E. Bowman.

The initial aims of the present series of papers are outlined. Acid-catalysed acidolysis of acylmalonic esters (IV) is shown to furnish the methyl ketones (VI) in high yield. Conditions have been found for the isolation of the intermediate β-keto-esters (V) in moderate yields.

Despite comparatively recent developments such as the use of cadmium dialkyls (Cason, *Chem. Reviews*, 1947, **40**, 15) and the general β-keto-ester synthesis devised by Breslow, Baumgarten, and Hauser (*J. Amer. Chem. Soc.*, 1944, **66**, 1286) a number of the more complex polyfunctional types of carbonyl compounds remain inaccessible. Whilst there can be little doubt that the method employing organo-cadmium compounds is convenient for preparing the simpler types of ketones, its general application is inevitably limited by the usual restrictions accompanying the use of Grignard reagents; on the other hand, methods involving the use of β-keto-esters are frequently unsatisfactory owing to low yields at one or more of the many stages involved, *viz.*, the synthesis of the β-keto-esters, mono- or di-alkylation, and eventual ketonic hydrolysis, sometimes under severe conditions (Renfrow, *J. Amer. Chem. Soc.*, 1944, **66**, 144).

Examination of the problem of developing a more general method suggested that a promising route lay in the simple metathetical reaction between acid chlorides and sodiomalonic esters, provided that the degradation of the β-keto-diester (I) could be realised.

$$R{\cdot}COCl + R'{\cdot}CNa(CO_2Et_2)_2 \longrightarrow \underset{\text{(I.)}}{R{\cdot}CO{\cdot}CR'(CO_2Et)_2} \longrightarrow R{\cdot}CO{\cdot}CH_2R'$$

Compounds (I) have been prepared on various occasions during the last fifty years but have rarely been used in synthetical operations owing to the ease with which they suffer disruption into their original components (except where R' = H) under the action of the normal hydrolytic reagents (Michael, *Amer. Chem. J.*, 1892, **14**, 510; Robinson and Robinson, *J.*, 1925, **127**, 175). The problem, therefore, resolved itself into that of finding conditions for generating the free acylmalonic acids from their esters whilst leaving intact the rest of the molecule, spontaneous or subsequent thermal decarboxylation of the keto-acid (II) to the ketone (III) being expected to occur quantitatively.

$$\text{(I)} \longrightarrow \underset{\text{(II.)}}{R{\cdot}CO{\cdot}CR'(CO_2H)_2} \longrightarrow \underset{\text{(III.)}}{R{\cdot}CO{\cdot}CH_2R'} + 2CO_2 \quad .$$

This and the subsequent paper report two different approaches to this problem, and in both cases new methods of ketone synthesis have been elaborated. Experiments on the removal of one carbethoxy-group from acylmalonic and the analogous acylcyanoacetic esters, with the object of obtaining β-keto-esters and β-keto-nitriles respectively, will be reported later.

Acidolysis of Acylmalonic Esters.—Acylmalonic esters (IV) are, in general, high-boiling, viscous liquids or low-melting solids existing mainly in the enolic form and hence readily soluble in aqueous alkalis, in which media they are readily hydrolysed to their progenitors (Michael, *loc. cit.*). Therefore, use of alkaline conditions to bring about ketonic hydrolysis offers little hope of success. In recent years, however, the required degradation has been realised by several groups of workers (Giacolone, *Gazzetta*, 1936, **65**, 1127; Adickes, *J. pr. Chem.*, 1943, **161**, 271; Fuller, Tonkin, and J. Walker, *J.*, 1945, 633; H. G. Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386) employing strong acids. The technique developed by Walker and Hauser, whereby the crude acylmalonic esters prepared from the acid chloride and ethoxymagnesiomalonic ester (Lund, *Ber.*, 1934, **67**, *B*, 935) are subjected to boiling aqueous sulphuric acid in acetic acid solution, has been shown to be extremely useful for the preparation of ketones $R{\cdot}CO{\cdot}CH_3$ where R is aromatic; the reaction failed completely when R was a straight-chain alkyl group such as *n*-amyl and for the fully substituted compounds (I; $R = NO_2{\cdot}C_6H_4$, $R' = Bu^n$).

It seemed possible that a more general solution to this problem might be realised by the use of acid-catalysed acidolysis according to the following scheme:

$$\begin{array}{lr} \text{(IV.)}\quad R{\cdot}CO{\cdot}CH(CO_2Et)_2 \underset{R'{\cdot}CO_2H}{\overset{H+}{\rightleftharpoons}} R'{\cdot}CO_2Et + R{\cdot}CO{\cdot}CH(CO_2H){\cdot}CO_2Et \xrightarrow{-CO_2} & R{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et\quad\text{(V.)} \\ & \Big\Updownarrow{\scriptstyle H+;\ R'{\cdot}CO_2H} \\ \text{(VI.)}\quad R{\cdot}CO{\cdot}CH_3 \xleftarrow{-CO_2} & R{\cdot}CO{\cdot}CH_2{\cdot}CO_2H + R'{\cdot}CO_2Et \end{array}$$

The initial experiments were carried out by refluxing a mixture of benzoylmalonic ester (1 mol.) and acetic acid (8 mols.) containing 1% sulphuric acid as catalyst. The expected reaction was found to occur with evolution of carbon dioxide and formation of acetophenone, benzoylacetic ester, and some unchanged starting material. Although the isolation of some β-keto-ester was highly satisfactory, attention at this stage of the work was focussed on the problem of forcing the reaction to completion. Substitution of propionic acid for acetic acid led to a considerable improvement in the yield of ketone although a small quantity of β-keto-ester still remained. Finally the technique of refluxing the acylmalonic ester (1 mol.) with propionic acid (5—8 mols.) and sulphuric acid (1% by weight of reactants) for 3 hours, followed by a short treatment with 10N-sulphuric acid to complete the hydrolysis of any residual β-keto-ester, was adopted. In this manner benzoylmalonic ester yielded acetophenone in practically quantitative yield.

Nevertheless, the isolation of the acylmalonic esters was both wasteful of materials and restrictive in scope in view of the high boiling points of even the lower members of the series and hence conditions were sought for obtaining the highest possible yield of crude acylmalonic esters. The technique employed by Walker and Hauser (*loc. cit.*) suffers from the disadvantage that the reaction is carried out in the presence of free ethanol employed in the formation of the magnesium derivative. It seemed that the presence of the latter, together with that inevitably formed in the reaction, would considerably lower the yield of keto-ester, particularly in the aliphatic series. The preparation of ethoxymagnesiomalonic ester was therefore effected in benzene solution, using only a slight excess of ethanol which was finally removed as its azeotrope with benzene; in this manner ethanol-free solutions of the magnesium complex were readily obtained. Treatment of this reagent (100% excess) with the requisite acid chloride, followed by recovery of excess of malonic ester by distillation, yielded the crude keto-diester which on acidolysis as above furnished the methyl ketone $R{\cdot}CO{\cdot}CH_3$ in very high yield.

In this manner the acid chlorides of octanoic, undecanoic, dodecanoic, stearic, sebacic, *o*-chlorobenzoic, and *p*-nitrobenzoic acids, and of methyl hydrogen sebacate gave the corresponding methyl ketones. Even in the aromatic series, as shown by the last two examples, the yields by this process are considerably higher than those obtained by Walker and Hauser (*loc. cit.*).

Preparation of β-keto-esters from the corresponding acylmalonic esters was first described by Bernhard (*Annalen*, 1894, **282**, 166) who obtained benzoylacetic ester by steam-distillation of benzoylmalonic ester. Breslow *et al.* (*loc. cit.*) obtained propionylacetic ester similarly but in very poor yield. Recently, two new methods have been elaborated; first, the general β-keto-ester synthesis of Breslow *et al.* (*ibid.*) using the rather inaccessible ethyl *tert.*-butylmalonate, and, secondly, thermal pyrolysis of acylmalonic esters in the presence of toluene- or naphthalene-sulphonic acid (Riegel and Lilienfield, *J. Amer. Chem. Soc.*, 1945, **67**, 1274).

The isolation of some of the intermediate β-keto-ester in the early experiments on the acidolysis of benzoylmalonic ester raised hopes that it might be possible to find conditions for obtaining the analogous aliphatic keto-esters. For this purpose a large quantity of lauroylmalonic ester was prepared and submitted in portions to the action of acetic acid (1 : 5) with various quantities of catalyst for various times. Limitation of time prevented a full examination of the reaction but under the best conditions found (3 hours at the boiling point using 0·22% sulphuric acid), a 48% yield of lauroylacetic ester (V; $R = C_{11}H_{23}$) and a 41% yield of the ketone (VI; $R = C_{11}H_{23}$) were obtained. A similar reaction applied to undec-10-enoyl chloride furnished ***ethyl* 3-*ketotridec*-12-*enoate*** * (V; $R = CH_2{:}CH{\cdot}[CH_2]_8$) (45%) and the ketone (VI; $R = CH_2{:}CH{\cdot}[CH_2]_8$) (41%). The reaction was finally investigated on a larger scale (1·25 mols.) using octanoyl chloride, ethyl 3-ketodecanoate (V; $R = C_7H_{15}$) (43%) together with methyl heptyl ketone (VI; $R = C_7H_{15}$) (52%) being obtained.

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* Geneva nomenclature is used throughout this paper.

Finally the acidolysis of fully substituted acylmalonic esters (I; R = R′ = alkyl) was investigated, but in no case could the desired reaction be brought about. The failure of Renfrow (*loc. cit.*) to bring about a similar reaction with fully substituted β-keto-esters, $CH_3·CO·CRR'·CO_2Et$, may be significant in this connexion. In the course of this work *ethyl* n-*butyl* iso*hexoylmalonate* (*6-keto-9-methyldecane-5 : 5-dicarboxylate*) (I; R = $(CH_3)_2CH·CH_2·CH_2$, R′ = Bu^n) was prepared.

EXPERIMENTAL.

Ethoxymagnesiomalonic Ester.—Magnesium (36 g., 1·5 mols.) was covered with dry benzene (110 ml.) containing absolute ethanol (10 ml.) in a three-necked flask fitted with a tap funnel and reflux condenser. After the addition of a crystal of iodine and/or carbon tetrachloride (1 ml.) a small portion of a solution (*A*) of ethyl malonate (commercial, undistilled; 240 g., 1·5 mols.), absolute ethanol (70 g., *i.e.*, 78 g. in all; 1·7 mols.) in dry benzene (300 ml.) was added and the mixture heated, if necessary, until a vigorous reaction set in. Solution (*A*) was then added at a convenient rate (2—3 hours) and the product refluxed until dissolution of the magnesium was complete. At this stage the reflux condenser was replaced by a fractioning column of the Widmer or Fenske type (30 cm. long) fitted with a reflux head, and the mixture was slowly distilled until most of the free ethanol had been removed as azeotrope with benzene (b. p. 68·4°) as shown by a tendency for the distillation temperature to rise to about 70°. The residue in the flask consisted of ethanol-free ethoxymagnesiomalonic ester in benzene solution (volume, approx. 700 ml.) and was ready for use.

Crude Acylmalonic Esters.—The requisite acid chloride (1 mol.) in dry benzene was added, with stirring and external cooling, to the benzene solution of ethoxymagnesiomalonic ester (2 mols.) during 30 minutes and the resulting mixture refluxed for 1 hour. The cooled solution was decomposed by addition to ice and dilute sulphuric acid, and the organic layer thoroughly shaken with more dilute sulphuric acid, followed by water (3 portions). Removal of the first portion of benzene from the dried solution (Na_2SO_4) was effected at room temperature under reduced pressure. The excess of malonic ester was then recovered by distillation at 0·5 mm. (bath-temperature up to 100°), in excellent yield. A fractionating column was not necessary at this stage when acids higher than heptanoic acid were used.

Complete Acidolysis.—A mixture of the crude acylmalonate (1 mol.), propionic acid (commercial; 8 mols.), and sulphuric acid (1% by weight of total weight of reactants) was boiled under reflux for 3 hours; a vigorous evolution of gas occurred in the early stages. Then sulphuric acid (75 ml. of 4N.) was added to the slightly cooled reaction mixture, and refluxing was continued until no further gas was evolved. The method of working up depended on the scale of the reaction and nature of the product.

Method A (*small scale*). The reaction product was poured into water, and the mixture neutralised by aqueous sodium hydroxide. The ketone, if solid, was then filtered off or, if liquid, taken up in a solvent and isolated in the usual manner. If the product was a keto-acid, it was extracted directly without neutralisation.

Method B (*small scale; non-volatile ketones*). The reaction mixture was poured into water, and steam passed into the mixture until the propionic acid was all removed. The product was then isolated from the residue as usual.

Method C (*large scale*). An excess (70% over that required for neutralisation of the sulphuric acid) of anhydrous sodium acetate was added to the acidolysis mixture which was then distilled under reduced pressure through a Vigreux column (20 cm. long) to remove ethyl propionate and most of the propionic acid. The residue was then worked up as described in method (A).

In this manner the following acid chlorides were converted into the respective methyl ketones.

Starting materials. Acid.	Acid chloride. B. p. or m. p.	Ketone, $R·CO·CH_3$. R.	Method.	B. p. or m. p.	Yield, %.
Octanoic	82°/15 mm.	*n*-Heptyl [1]	(C)	80°/10 mm.	93
Undecanoic	95°/15 mm.	*n*-Decyl [2]	(A)	107°/5 mm.	94
Lauric	136°/10 mm.	*n*-Undecyl [3]	(A)	27—28°	97
Stearic [4]	—	*n*-Heptadecyl [5]	(B)	55—56°	96
Sebacic	140°/1 mm.	*n*-9-Ketodecyl [6]	(A)	69°	93
Methyl hydrogen sebacate [7]	—	ω-Carboxyoctyl [9]	(B)	56°	100 [8]
o-Chlorobenzoic	90°/10 mm.	*o*-Chlorophenyl [10]	(A)	84°/3 mm.	98
p-Nitrobenzoic	72°	*p*-Nitrophenyl [12]	(B)	75—78°	99 [11]

[1] Semicarbazone, m. p. 117—118° (Dakin, *Amer. Chem. J.*, 1910, **44**, 46, reported m. p. 118°). [2] Semicarbazone, m. p. 122—123° (Pickard and Kenyon, *J.*, 1911, **99**, 57, gave m. p. 122—123°). [3] Semicarbazone, m. p. 117° (Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 685, and Asahina and Nakayama, *J. Pharm. Soc. Japan*, 1925, **52**, 65, gave m. p.s 115—116° and 118—119° respectively). [4] Crude: prepared from the acid and thionyl chloride, with removal of the latter *in vacuo*. [5] Oxime, m. p. 77° (Thoms and Vogelsang, *Annalen*, 1907, **357**, 161, reported m. p. 77°). [6] Dodecane-2 : 11-dione, slender needles [from light petroleum (b. p. 40—60°)], m. p. 69° (Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 46, reported m. p. 67·4—67·8°) (Found: C, 72·4; H, 10·8. Calc. for $C_{12}H_{22}O_2$: C, 72·7; H, 11·1%). The *dioxime* crystallised from ethyl acetate and then benzene in prisms, m. p 114—115° (Found: N, 11·9. $C_{12}H_{24}O_2N_2$ requires N, 12·3%). [7] *Org. Synth.*, 1945, **25**, 71. [8] Crude. [9] Crystallised from benzene; m. p. 58° (Abraham, Mowat, and Smith, *J.*, 1937, 948, gave m. p. 59°); semicarbazone, m. p. 135° (*idem, ibid.*, m. p. 135—136°). [10] Semicarbazone, m. p. 159° (Wahl and Rolland, *Ann. Chim.*, 1928, [x], **10**, 29, reported m. p. 159—160°). [11] Crude. [12] Crystallised from benzene–light petroleum (b. p. 40—60°); m. p. 80° (Drewsen, *Annalen*, 1882, **212**, 160, gave m. p. 80—81°); oxime, m. p. 172° (Posner, *ibid.*, 1912, **389**, 43, gave m. p. 172—173°).

Partial Acidolysis. Preparation of β-Keto-esters.—The following conditions gave the best results: The crude acylmalonate (as above; 1 mol.), glacial acetic acid (5 mols.), and sulphuric acid (0·22% by weight of reactants) were boiled under reflux for 3 hours. Excess of barium carbonate (5 times the wt. of sulphuric acid) was then added to the cooled reactants, and the mixture set aside with occasional agitation for 1 hour. After filtration, the filtrate was carefully fractionated *in vacuo* in the presence of a trace of barium carbonate, through a Vigreux column.

Ethyl 3-Ketotetradecanoate.—In this manner lauroylmalonic ester (crude; 0·1 mol.) gave methyl undecyl ketone, b. p. 110—112°/5 mm. (8·7 g., 44%), and the keto-ester as a colourless oil, b. p. 128—130°/0·2 mm., n_D^{20} 1·4489 (13 g., 48%) (Found: C, 70·6; H, 10·8. Calc. for $C_{16}H_{30}O_3$: C, 71·1; H, 11·1%). The latter ester gave a deep-red ferric reaction and formed a *pyrazolone* which separated from methanol and then light petroleum (b. p. 40—60°) in colourless prisms, m. p. 67° (Found: N, 11·0. $C_{20}H_{30}ON_2$ requires N, 10·8%).

Ethyl 3-Ketodecanoate.—Crude octanoylmalonic ester (1·25 mols.) similarly furnished methyl heptyl ketone (93 g., 52%) and the keto-ester as a colourless oil, b. p. 84—86°/0·2 mm., n_D^{20} 1·4390, which gave a deep-red colour with aqueous-alcoholic ferric chloride (Found: C, 66·8; H, 10·0. Calc. for $C_{12}H_{22}O_3$: C, 67·3; H, 10·4%) (yield: 112 g., 43%). The pyrazolone separated from methanol and then light petroleum (b. p. 40—60°) in colourless prisms, m. p. 82° (Breusch and Keskin, *Rec. Fac. Sci. Univ. Istanbul*, 1946, **11**, *A*, 24, reported m. p. 82°) (Found: N, 9·0. Calc. for $C_{16}H_{22}ON_2$: N, 8·9%).

Ethyl 3-Ketotridec-12-enoate.—Undec-10-enoyl chloride (b. p. 98°/3 mm.; 41 g., 0·2 mol.) was treated with ethoxymagnesiomalonic ester (0·4 mol.), and the crude product partly acidolysed according to the general method. In this manner, dodec-11-en-2-one (15 g., 41%), b. p. 104°/5 mm. (semicarbazone, m. p. 122—123°), and *ethyl 3-ketotridec-12-enoate*, a colourless oil (23 g., 45%), b. p. 122—124°/0·4 mm., n_D^{20} 1·4485 (Found: C, 70·5; H, 10·6. $C_{15}H_{26}O_3$ requires C, 70·9; H, 10·2%), were obtained. The latter gave a deep-red ferric colour and formed a *copper* derivative which separated from ice-cold light petroleum (b. p. 40—60°) in pale green, slender needles, m. p. 75—77° [Found: Cu, 10·9. $Cu(C_{15}H_{25}O_3)_2$ requires Cu, 11·2%].

Ethyl 6-Keto-9-methyldecane-5 : 5-dicarboxylate.—Prepared in the usual manner (cf. Michael, *loc. cit.*) from *iso*hexanoyl chloride and sodio-*n*-butylmalonic ester in ether, the *ester* was obtained as a colourless viscous oil, b. p. 120°/0·5 mm., n_D^{20} 1·4408 (Found: C, 64·9; H, 9·7. $C_{17}H_{30}O_5$ requires C, 65·0; H, 9·8%).

BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, October 21st,* 1949.]

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71. *Experiments on the Synthesis of Carbonyl Compounds. Part II. A General Synthesis of Saturated Ketones,* R·CO·CH₂R′.

By R. E. BOWMAN.

The benzyl esters of acylmalonic acids (II) undergo hydrogenolysis with the formation of the parent keto-acids, which readily lose two molecules of carbon dioxide to give the corresponding ketones, R·CO·CH₂R′. The reaction appears to be of general application subject only to the absence of reducible substituents. A preliminary account of this work has already been published (*Nature*, 1948, **162**, 111).

IN the preceding paper a method of converting acylmalonic esters, $R{\cdot}CO{\cdot}CH(CO_2Et)_2$, into the ketones $R{\cdot}CO{\cdot}CH_3$ by acidolysis was described. Failure to extend this reaction to the fully substituted compounds $R{\cdot}CO{\cdot}CR(CO_2Et)_2$ demonstrated the need of an entirely new approach to the problem. The hydrogenolytic fission of benzyl esters appeared to offer an alternative method of developing a general ketone synthesis as follows:

$$CH_2(CO_2{\cdot}CH_2Ph)_2 \longrightarrow R'{\cdot}CH(CO_2{\cdot}CH_2Ph)_2 \longrightarrow \underset{\text{(I.)}}{R'{\cdot}CNa(CO_2{\cdot}CH_2Ph)_2} \xrightarrow{R{\cdot}COCl}$$

$$R{\cdot}CO{\cdot}CR'(CO_2{\cdot}CH_2Ph)_2 \xrightarrow{H_2\text{-}Pd} R{\cdot}CO{\cdot}CR'(CO_2H)_2 \longrightarrow R{\cdot}CO{\cdot}CH_2R' + 2CO_2$$

A critical examination of this route served to emphasise the difficulties likely to be encountered in the first stage of the synthesis owing, in particular, to the high boiling points (*e.g.*, benzyl malonate boils at *ca.* 170°/0·5 mm.) and low crystallising powers associated with benzyl esters in general: furthermore, there was also the possibility of some hydrogenolysis of the benzyl groups during the second stage of the process. Consideration of the possibilities involved, however, suggested that these difficulties might be avoided by forming the sodio-benzyl ester (I) *in situ* from the corresponding ethyl ester by ester interchange with benzyl alcohol in benzene solution, the sodium enol acting as catalyst for the interchange and the reaction being forced to completion by removal of the ethanol formed as its azeotrope with benzene. The next stages in the procedure would then consist of coupling of the sodio-derivative (I) with the requisite acid chloride, catalytic debenzylation of the resulting keto-ester (II), and finally thermal decarboxylation of the acid (III) to the ketone (IV):

$$\text{(I)} + \mathrm{R{\cdot}COCl} \longrightarrow \underset{\text{(II.)}}{\mathrm{R{\cdot}CO{\cdot}CR'(CO_2{\cdot}CH_2Ph)_2}} \xrightarrow{4H} \underset{\text{(III.)}}{\mathrm{R{\cdot}CO{\cdot}CR'(CO_2H)_2}} \longrightarrow \underset{\text{(IV.)}}{\mathrm{R{\cdot}CO{\cdot}CH_2R'}}$$

This idea was first put to test using ethyl ethane-1 : 1 : 2-tricarboxylate (I; $R'=CH_2{\cdot}CO_2Et$) which was converted into its sodio-derivative in benzene in the usual manner and treated with benzyl alcohol (3 mols.). Ester interchange was found to proceed readily as shown by the elimination of ethanol which was obtained (as azeotrope with benzene) with the aid of a fractionating column in almost theoretical yield. The resulting tribenzyl sodio-ester (I; $R' = CH_2{\cdot}CO_2{\cdot}CH_2Ph$) was then coupled with undecanoyl chloride, and the crude keto-ester (II; $R = n\text{-}C_{10}H_{21}$, $R' = CH_2{\cdot}CO_2{\cdot}CH_2Ph$) submitted to catalytic debenzylation using palladised charcoal at atmospheric pressure and temperature in ethanolic solution. Considerable difficulties were encountered at this stage owing to catalyst poisoning, but eventually most of the required hydrogen was absorbed. Decarboxylation of the product proceeded smoothly at, or just below, the boiling point of the solvent (ethanol), the expected product, 4-ketotetradecanoic acid * (IV; $R = C_{10}H_{21}$, $R' = CH_2{\cdot}CO_2H$) being obtained in 66% yield.

At this stage of the work, attention was focussed on the purely practical aspects of the problem, namely, the purification of commercial benzyl alcohol and the finding of more effective catalysts. Initially, debenzylations were carried out in alcohol with palladised charcoal (iron-free) as catalyst; later mixtures of the latter and palladised strontium carbonate were used. More recently (unpublished results) the use of palladised strontium carbonate (10% of Pd) in ethyl acetate has been found to be most effective and is now the preferred procedure. As the result of these and subsequent experiments a general technique has been evolved and is described in full in the Experimental section.

By use of this technique, *n*-octanoyl chloride and *n*-octylmalonic ester yielded *heptadecan-8-one* (IV; $R = C_7H_{15}$, $R' = C_8H_{17}$) (91%) which was characterised as the substituted *hydantoin* (Henze, *J. Amer. Chem. Soc.*, 1942, **64**, 522), and similarly *2-methylpentadecan-5-one* [IV; $R = C_{10}H_{21}$, $R' = (CH_3)_2CH{\cdot}CH_2{\cdot}CH_2$] (80%) was obtained as an oil which resisted our attempts at characterisation.

Sebacoyl chloride and *n*-octylmalonic ester (2 mols.) furnished *octacosane*-10 : 19-*dione* (V) in 78% yield, characterised as the *dioxime* and by reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) to the saturated paraffin, *n*-octacosane, together with the product of partial reaction, the known 10-ketononadecanoic acid (VI).

(V.) $C_9H_{19}{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO{\cdot}C_9H_{19}$ $C_9H_{19}{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO_2H$ (VI.)

(VIII.) $C_4H_9{\cdot}CHEt{\cdot}CO{\cdot}[CH_2]_{11}{\cdot}CO_2H$ $OH{\cdot}CHPh{\cdot}CO{\cdot}C_{13}H_{27}$ (IX.)

The failure of the G. M. Robinson ketone synthesis (*J.*, 1930, 745) when applied to the preparation of α-substituted ketones (*Ann. Reports*, 1939, **36**, 300), and the low yields encountered in the use of the cadmium di-*sec.*-alkyls (Cason, *J. Amer. Chem. Soc.*, 1946, **68**, 2078), made it of interest to determine whether any such steric factors would operate in the debenzylation reaction. Accordingly 2-ethylhexanoyl chloride was condensed with benzyl sodioundecane-1 : 1 : 11-tricarboxylate, and the product debenzylated and decarboxylated to yield 13-*keto*-14-*ethyloctadecanoic acid* (VIII) in 78% yield (crude); this acid was purified through its *ethyl* ester and characterised as the p-*phenylphenacyl* ester.

Attention was next turned to the synthesis of ketones containing groups other than alkyl or carboxy-groups. ω-Hydroxyundecanoic acid was converted by successive treatment with acetyl chloride and oxalyl chloride into the ω-acetoxy-acid chloride which, without isolation, was coupled with benzyl sodio-*n*-octylmalonate (I; $R' = C_8H_{17}$) and furnished in the same manner 11-*ketoeicosanol*, $C_9H_{19}{\cdot}CO{\cdot}[CH_2]_{10}{\cdot}OH$, characterised as the *oxime* and by reduction (Clemmensen) to the known eicosanol. Acetylmandeloyl chloride and benzyl sodio-*n*-dodecylmalonate gave, by the general procedure, 1-*hydroxy*-1-*phenylpentadecan*-2-*one* (IX) in 65% yield. (IX) was characterised by oxidation with chromic acid (cf. Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, 1947, **30**, 1741) to the *diketone* and by reaction of the latter with *o*-phenylenediamine to give a *quinoxaline*.

Finally, as an example in the aromatic series, *m*-anisoyl chloride and benzyl sodioethane-1 : 1 : 2-tricarboxylate were condensed, and the product debenzylated and decarboxylated to yield the known γ-keto-γ-*m*-methoxyphenylbutyric acid. The investigation is being continued.

* Geneva nomenclature is used throughout this paper.

EXPERIMENTAL.

Apparatus.—All-glass apparatus fitted with ground-glass joints lubricated with silicone grease was used. The fractionating column used in the ester interchanges contained a packed section (40 × 1·8 cm.) of single-turn glass helices (Fenske) and was fitted with a total condensation–partial take-off head of the Whitmore–Lux pattern.

Reagents.—*Benzene.* The benzene used in these experiments was commercial AnalaR benzene which had been stored over sodium wire.

Benzyl alcohol. Commercial "pure" benzyl alcohol was mixed with Raney nickel (5% w/w) and the mixture heated on the steam-bath for 3 hours with occasional agitation. After cooling, the alcohol was decanted from the bulk of the metal and distilled under reduced pressure. The distillate usually contained benzaldehyde which was separated by careful fractionation under reduced pressure in an atmosphere of nitrogen or by oximation followed by distillation.

Palladium–charcoal catalyst. The catalyst was prepared in the manner described in *Org. Synth.*, 1946, **26**, 78 (catalyst D), with two modifications. First, the iron was removed from the charcoal with 6N-hydrochloric acid and, secondly, hydrogen was thoroughly removed by evacuation from the reduction mixture *at the final stage* of preparation before air was admitted. This procedure allows drying of the catalyst at 120° without ignition.

Palladised strontium carbonate (ca. 10% of Pd). Palladous chloride (8·9 g.) was dissolved in AnalaR concentrated hydrochloric acid (21 ml.) at the b. p., and the solution, after dilution with water (400 ml.), added with vigorous stirring to a suspension of strontium carbonate ("precipitated"; 70 g.) in water (500 ml.) during 5 minutes. The temperature of the stirred mixture was then raised to 80° during 15 minutes, and the solid allowed to settle. The supernatant liquid was removed by syphoning and washing (5 l.) carried out in the same manner. The catalyst was then removed by filtration, dried at 120°, and finely powdered.

Acid chlorides. Unless otherwise specified, acid chlorides were prepared in the usual manner from the acid and thionyl chloride, except that a considerable amount of first runnings was rejected to avoid contamination with sulphur-containing substances.

General Methods.—*Preparation of benzyl sodiomalonates.* The requisite ethyl sodiomalonates were prepared by two methods. (*a*) The ethyl malonate in benzene solution was added in the usual manner to sodium which had been powdered under pure toluene or xylene, the solvent decanted, and the residue washed several times with AnalaR benzene. (*b*) Clean sodium (1 mol.) was dissolved in magnesium-dried ethanol (20 × wt. of sodium), and the solution distilled from a flask fitted with tap-funnel (guard-tube) and condenser leading to a Kon rectangle, in an oil-bath heated to 190°. When most of the ethanol had distilled off and a slight crust had formed on the surface of the residue, the pressure in the flask was rapidly lowered, resulting in the rapid removal of solvent and the production of a solid foam of sodium ethoxide. The oil-bath was then removed and the ethoxide allowed to cool *in vacuo*. The system was closed by means of the appropriate taps and the malonic ester (1 mol.) in benzene solution added from the tap-funnel. Formation of the sodium enol was immediate as shown by dissolution of the sodium ethoxide; air was then admitted through the guard-tube. Benzyl alcohol (1 mol. per carbalkoxy-group in the malonic ester) was added to the foregoing solution, and the mixture distilled through the fractionating column already described, under a reflux-ratio of about 5 : 1 so that the temperature did not rise above 69°/760 mm. The distillation of benzene–ethanol azeotrope was rapid at first but gradually slowed down towards the end of the interchange when distillation was carried out under a higher reflux-ratio (20 : 1) at about 1—3 drops per minute, the temperature gradually rising to *ca.* 79°. At this stage the interchange was considered complete, and the residue which consisted of a benzene solution of benzyl sodiomalonate was allowed to cool.

Method (*a*) was used in the preliminary experiments as it allowed the interchange to be followed quantitatively but later, when this was found to be substantially complete under the conditions employed, the second method was always used since, in practice, it was more convenient and furnished a cleaner product.

Benzyl acylmalonates. The acid chloride (0·98 mol.) in benzene solution was added to the benzene solution of the benzyl sodiomalonate (1 mol.), with stirring or shaking, during a few minutes, and the mixture refluxed for a further 30 minutes. The cooled reaction mixture was then added to ice-water containing a trace of sulphuric acid, and the organic layer separated. The aqueous layer was extracted with fresh benzene and the combined benzene extracts washed with water and dried (Na_2SO_4). Removal of solvent was carried out at room temperature under reduced pressure until all water had distilled off, and was finally completed at 100°/0·5 mm. The products were yellow or yellow-brown viscous oils.

Debenzylation and decarboxylation of benzyl acylmalonates. The foregoing product (0·5 mol.) was dissolved in absolute ethanol or a mixture of ethanol and ethyl acetate (solvent volume, *ca.* 200 ml.), and stirred in an atmosphere of hydrogen in the presence of palladised charcoal (10% of Pd; 4 g.) until absorption became slow owing to poisoning of the catalyst (frequently 1 l. taken up). At this stage the catalyst was either removed by filtration and fresh charcoal catalyst added, or palladised strontium carbonate (10% of Pd; 5 g.) was added to the hydrogenation mixture, and the hydrogenation continued. If the first procedure was adopted, it was sometimes necessary to repeat the process, rates of up to 200 ml. per minute being realised; with the second method somewhat slower rates (*e.g.*, 60 ml. per minute) of hydrogen absorption occurred. The temperature of the reaction mixture was kept below 30° by external cooling. Furthermore, it was found on occasions that the hydrogenation became slow owing to premature decarboxylation, and accordingly the flask was evacuated and refilled with fresh hydrogen before the addition of fresh catalyst. When the hydrogenation was complete, the catalyst was removed by filtration, and the filtrate raised to the b. p. under a reflux condenser, whereupon brisk evolution of carbon dioxide took place. On completion of this stage (30 minutes), the solvent was distilled off and the product isolated.

4-Ketotetradecanoic Acid.—Undecanoyl chloride (b. p. 95°/2 mm.; 25·1 g., 0·122 mol.) was treated with the sodium enol of benzyl ethane-1 : 1 : 2-tricarboxylate (0·125 mol.) prepared from the ethyl ester (30·75 g., 0·125 mol.), sodium (2·9 g., 0·125 mol.) and benzyl alcohol (40·5 g., 0·375 mol.), and the product debenzylated and decarboxylated as described above. The product, after removal of solvent, was a semi-solid mass which was triturated with cold toluene (50 ml.). The solid (14 g.) was removed and the filtrate evaporated in an oil-bath at 170° to remove solvent and to decarboxylate any free ethanetricarboxylic acid. When cold, the residue was dissolved in ethyl acetate (100 ml.), and the solution washed with water and evaporated to dryness. Trituration of the residue with cold light petroleum (b. p. 40—60°) containing benzene (1%) furnished a further crop (6 g.). In this manner the total yield of crude keto-acid, m. p. 84—85°, was 20 g. (66%). The acid separated from benzene–light petroleum (b. p. 60—80°) in colourless plates, m. p. 87°; Robinson and Robinson (*J.*, 1926, 2206) give m. p. 87°. The oxime separated from light petroleum (b. p. 60—80°)–benzene (trace) in prisms, m. p. 74°, as described by the same authors.

Heptadecan-8-*one*.—The reactants were *n*-octoyl chloride (b. p. 81—82°/16 mm.; 19·9 g., 0·122 mol.) and benzyl sodio-*n*-octylmalonate (ethyl ester; 34 g., 0·125 mol.). The product was dissolved in light petroleum (b. p. 40—60°; 100 ml.) containing benzene (30 ml.), and the mixture treated with 2N-sodium hydroxide until alkaline. The organic layer was separated and the aqueous layer extracted again (2 × 50 ml. of same solvent mixture). The bulked extracts were washed with water and dried (Na_2SO_4), and the solvent removed by distillation, eventually, at 100°/0·2 mm. (to constant weight). The product readily solidified on cooling and was substantially pure *ketone* (28·2 g., 91%), m. p. 39—41°. It crystallised readily from methanol in colourless plates, m. p. 42° (Found: C, 80·4; H, 13·4. $C_{17}H_{34}O$ requires C, 80·3; H, 13·4%). The derived *hydantoin* (Henze, *loc. cit.*) separated from methanol in colourless tablets, m. p. 123° (Found: N, 8·3. $C_{19}H_{36}O_2N_2$ requires N, 8·6%).

2-*Methylpentadecan*-5-*one*.—The *ketone* was obtained in the same manner as in the previous experiment, from undecanoyl chloride (25·1 g., 0·122 mol.) and benzyl sodio*iso*butylmalonate, as a colourless oil, b. p. 134—136°/2 mm., m. p. 9—10°, n_{D}^{20} 1·4408 (23·4 g., 80%) (Found: C, 79·7; H, 13·2. $C_{16}H_{32}O$ requires C, 80·0; H, 13·3%). Attempts to prepare crystalline derivatives failed.

Octacosane-10 : 19-*dione*.—Sebacoyl chloride (b. p. 140°/1 mm.; 15 g., 0·062 mol.) was caused to react with benzyl sodio-*n*-octylmalonate (0·125 mol.) prepared as previously, and the product debenzylated and decarboxylated in the usual manner in ethanol–ethyl acetate solution (100 ml. : 50 ml.). The solution obtained after decarboxylation, furnished, on cooling, 15 g. of the ketone. Concentration of the filtrate to 25 ml. furnished a second crop (5·5 g.), the total yield of crude material, m. p. 92—94°, being 78%. *Octacosane*-10 : 19-*dione* separated from methanol as colourless plates, m. p. 95° (Found: C, 79·2; H, 12·6. $C_{28}H_{54}O_2$ requires C, 79·6; H, 12·8%). The *dioxime* crystallised from ethyl acetate in colourless prisms which melted at 68°, resolidified, and finally remelted at 78° (Found: N, 6·3. $C_{28}H_{56}O_2N_2$ requires N, 6·2%). A sample of the ketone was subjected to the modified Wolff–Kishner reduction (Huang-Minlon, *loc. cit.*), to give *n*-octacosane, colourless plates (from ethanol), m. p. 64° (lit., 64—65°).

The filtrate from the second crop of ketone was diluted with water (5 ml.) and neutralised hot with sodium hydroxide (4N.); on cooling, the sodium salt of the keto-acid separated (2·7 g.). The free acid, 10-ketononadecoic acid, obtained in the usual manner, crystallised from light petroleum (b. p. 80—100°) in colourless plates, m. p. 86—87°. Robinson and Robinson (*loc. cit.*) gave m. p. 86—87°. The oily oxime was treated with sulphuric acid to give the derived amide, m. p. 83°.

13-*Keto*-14-*ethyloctadecanoic Acid*.—A sample of 2-ethylhexanoic acid (Messrs. British Industrial Solvents, Ltd.) was converted into its acid chloride (b. p. 76°/20 mm.), and the latter (16·0 g., 0·098 mol.) treated with benzyl sodioundecane-1 : 1 : 11-tricarboxylate (0·1 mol.). The oily product obtained in the usual manner was refluxed with acetic acid (50 ml.) containing sulphuric acid (2 ml.; 20N.) for 30 minutes to decompose any keto-ester present. After dilution with water, the mixture was steam-distilled until free from steam-volatile materials, and the residual oil isolated with ether. The residue was extracted with light petroleum (b. p. 40—60°; 400 ml.) at 0°. Evaporation of the light petroleum extract furnished the crude keto-acid (25·5 g., 78%) which was substantially pure since it was solid at room temperature (22°). A sample (10 g.) was purified by conversion into its *ethyl* ester (by azeotropic esterification), which distilled as a colourless oil, b. p. 186—192°/0·2 mm., n_{D}^{20} 1·4480 (Found: C, 74·0; H, 11·6. $C_{22}H_{42}O_3$ requires C, 74·6; H, 11·9%).

The ester was hydrolysed with boiling aqueous-alcoholic sodium hydroxide (N.), and the free *keto-acid* isolated as a colourless oil, b. p. 203—204°/0·3 mm., m. p. 24—25·5° (thermometer in liquid; faintly cloudy melt), n_{D}^{25} 1·4580 (Found: C, 73·4; H, 11·7. $C_{20}H_{38}O_3$ requires C, 73·6; H, 11·7%). It formed a p-*phenylphenacyl* ester which separated from moist ethanol (norite) at 0° in interlocking colourless needles, m. p. 43° (Found: C, 78·2; H, 9·1. $C_{34}H_{50}O_4$ requires C, 78·6; H, 9·4%).

11-*Ketoeicosanol*.—11-Hydroxyundecanoic acid (24·8 g., 0·122 mol.) was dissolved in dry AnalaR benzene (50 ml.), and acetyl chloride (13 ml.) added during 10 minutes. The solution was then refluxed for a further 10 minutes, and the solvent and excess reagent were removed by distillation under reduced pressure. The residual acetoxy-acid was dissolved in fresh, dry AnalaR benzene (50 ml.), and oxalyl chloride (45 g., 0·35 mol.) added. After the vigorous reaction had subsided, the mixture was refluxed on the steam-bath for 0·5 hour, and solvent and unchanged chloride removed by distillation under reduced pressure, eventually at 90°/0·5 mm. The yield of crude acetoxyundecanoyl chloride was 33·0 g. (calc., 32·2 g.). The chloride in benzene solution was brought into reaction with benzyl sodio-*n*-octylmalonate (0·125 mol.), and the reaction product isolated as described for heptadecan-8-one. The product remaining after evaporation of the solvent was hydrolysed with boiling alcoholic potassium hydroxide (N.; 100% excess) and isolated by dilution with water. 11-*Ketoeicosanol* was thus obtained as a white solid (22·9 g., 60%), m. p. 74—76°, which crystallised from ethanol and then light petroleum (b. p. 60—80°) in interlocking needles, m. p. 77° (Found: C, 76·8; H, 12·6. $C_{20}H_{40}O_2$ requires C, 76·9; H, 12·8%). It was characterised as the *oxime* which separated from benzene–light petroleum (b. p. 40—60°) at 0° in slender needles, m. p. 38—38·5° (Found: N, 4·4. $C_{20}H_{41}O_2N$ requires N, 4·3%), and by Clemmensen reduction in the usual manner to *n*-eicosanol, prisms (from methanol), m. p. 64—65° (Levene and Taylor, *J. Biol. Chem.*, 1924, **59**, 915, reported m. p. 65—65·5°).

1-*Hydroxy*-1-*phenylpentadecan*-2-*one*.—Acetylmandelyl chloride (34·8 g., 0·163 mol.) was condensed with benzyl sodio-*n*-dodecylmalonate (0·167 mol.) as before. The residue obtained after decarboxylation and removal of solvent was dissolved in light petroleum (b. p. 40—60°)–ethyl acetate (1 : 1), and the mixture made alkaline with aqueous sodium hydroxide. Considerable difficulty in separation of the phases owing to emulsification was encountered, but eventually the extraction was completed. The combined organic extracts (500 ml.) were washed with water, and the solvent was removed by distillation. The residue was gently warmed with aqueous alcoholic sodium hydroxide (N.; 0·16 mol.) for 15 minutes, and the product isolated by dilution with water. The crude *acyloin* (35 g., 65%), m. p. 50—53°, was slightly yellow, owing presumably to the presence of the corresponding diketone. It was crystallised several times from methanol and then light petroleum (b. p. 40—60°), whence it separated as tiny colourless prisms, m. p. 60° (Found : C, 78·8; H, 10·9. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·7%).

The acyloin (1·5 g.) in acetic acid (20 ml.) containing sulphuric acid (2 ml. of 20N.) was treated dropwise at room temperature with chromic acid (10N.) until the solution assumed a permanent orange-red colour. Dilution with water afforded the product as a yellow oil which readily solidified. Crystallisation from methanol at 0° and then from light petroleum (b. p. 40—60°) furnished the *diketone* as yellow plates, m. p. 52—53° (Found : C, 79·3; H, 10·4. $C_{21}H_{32}O_2$ requires C, 79·6; H, 10·2%). The diketone (1·58 g., 0·05 mol.) and *o*-phenylenediamine (0·54 g., 0·05 mol.) were refluxed in methanolic solution (10 ml.) for 5 minutes. The solution, on cooling, deposited the *quinoxaline* (0·9 g.), m. p. 62°, which separated from methanol (norite) in colourless felted needles, m. p. 62—63° (Found : N, 7·2. $C_{27}H_{36}N_2$ requires N, 7·8%).

γ-*Keto*-γ-m-*methoxyphenylbutyric Acid*.—*m*-Anisoyl chloride (b. p. 96—97°/3 mm.; 16·3 g., 0·095 mol.) was treated with benzyl sodioethane-1 : 1 : 2-tricarboxylate (0·1 mol.) in the usual manner. The product, after debenzylation, decarboxylation, and removal of solvent, was boiled with sodium hydroxide (200 ml.; 2N.) for 30 minutes and the cooled solution acidified with excess of sulphuric acid (20N.). The acid (16·35 g., 83%; m. p. 100—102°) crystallised from aqueous alcohol (norite) in long needles, m. p. 110°. The semicarbazone separated slowly from its reaction mixture (aqueous-alcoholic solution) in needles, m. p. 177°. Thompson (*J.*, 1932, 2314) gave m. p. 111° and 177° respectively for the keto-acid and its semicarbazone.

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72. *Experiments on the Synthesis of Carbonyl Compounds. Part III. Addition of Ethyl Acetoacetate to Ethyl Sorbate.*

By D. E. AMES and R. E. BOWMAN.

Addition of ethyl acetoacetate to ethyl sorbate has been realised and the product (I) reduced and degraded to (±)-7-*keto*-5-*methyloctanoic acid* (III). The structure of (III) has been proved by reduction to (±)-5-*methyloctanoic* acid (IV) which has been synthesised by an independent route.

IN connection with another investigation we wished to prepare 7-keto-5-methyloctanoic acid, $CH_3CO{\cdot}CH_2{\cdot}CH{\cdot}Me{\cdot}[CH_2]_3{\cdot}CO_2H$. It seemed possible that a convenient method for the preparation of this material was by way of the keto-diester (I) which would result from a Michael addition of ethyl acetoacetate to ethyl sorbate :

$$\begin{tikzcd}
CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et + CHMe{:}CH{\cdot}CH{:}CH{\cdot}CO_2Et \arrow[r] & CH_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2Et \quad \text{(I.)} \arrow[d] \\
\text{(III.)} \quad CH_3{\cdot}CO{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2H & CH_3{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2Et \quad \text{(II.)} \arrow[l]
\end{tikzcd}$$

There appears to be no recorded instance in the literature of the addition of ethyl acetoacetate to sorbic esters, although malonic and cyanoacetic esters have been used and been found to give products corresponding, predominantly, to 1 : 4-addition (Vorländer, *Annalen*, 1906, **345**, 228; Kohler and Butler, *J. Amer. Chem. Soc.*, 1926, **48**, 1036; Farmer and Healey, *J.*, 1927, 1060; Farmer and Mehta, *J.*, 1930, 1610; Bloom and Ingold, *J.*, 1931, 2765).

In *tert.*-butanolic solution in the presence of potassium *tert.*-butoxide the reaction furnished the unsaturated *keto*-diester (I) in excellent yield. This was catalytically reduced with the aid of palladised strontium carbonate to the corresponding saturated *keto*-diester (II) which on hydrolysis with constant-boiling hydrochloric acid yielded (±)-7-*keto*-5-*methyloctanoic acid* (III), characterised as its *semicarbazone*, p-*bromophenacyl* and *ethyl* ester. The structure and homogeneity of (III) were proved by unequivocal synthesis of the corresponding saturated acid (IV) (p-*bromophenacyl* ester), obtained in almost theoretical yield by the modified Wolff–Kishner reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) and synthesised as follows.

$$\underset{\text{(V.)}}{CH_3{\cdot}CO{\cdot}[CH_2]_3{\cdot}Cl} \xrightarrow{PrMgBr} \underset{\text{(VI.)}}{CH_3{\cdot}CPr{:}CH{\cdot}[CH_2]_2{\cdot}Cl} \xrightarrow{H_2\text{-}PtO_2} \underset{\text{(VII.)}}{CH_3{\cdot}CHPr{\cdot}[CH_2]_3{\cdot}Cl} \xrightarrow[KOH]{KCN\text{-}}$$

$$CH_3{\cdot}CHPr{\cdot}[CH_2]{\cdot}_3CO_2H \quad \text{(IV.)}$$

1-Chloropentan-4-one (V) and *n*-propylmagnesium bromide (cf. Cason, Brewer, and Pippen, *J. Org. Chem.*, 1948, **13**, 239—248) gave *5-methylhept-4-enyl chloride* (VI), separated from unchanged ketone by oximation of the ketone, followed by distillation, and then reduced using Adams's catalyst and treated, without isolation, with potassium cyanide and then sodium hydroxide to give (±)-*5-methyloctanoic acid*, identical with the acid resulting from (III).

The evidence presented herein leaves, in our opinion, no doubt of the homogeneity or structure of (III). For the keto-esters (I) and (II) the position is not so clear, as complete absence of the analogous products formed by 1 : 2-addition cannot be assumed.

EXPERIMENTAL.

*Ethyl 6-Keto-5-methylhept-2-ene-*1 : *5-dicarboxylate.*—Ethyl acetoacetate (98 g., 0·75 mol.) and ethyl sorbate (53 g., 0·38 mol.) were added to absolute *tert.*-butanol (150 ml.) in which potassium (2·5 g.) had been dissolved, and the mixture was refluxed in an oil-bath at 110—120° for 12 hours. The cold solution was poured into dilute sulphuric acid, and the oil taken up in benzene. After removal of the solvent and unreacted materials by distillation, the *ethyl* ester was obtained as an almost colourless oil (78 g., 75%), b. p. 120°/0·5 mm., n_D^{20} 1·4530 (Found : C, 61·9; H, 8·2. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%). It gave a deep-red colour with aqueous-alcoholic ferric chloride and absorbed bromine with great avidity.

*Ethyl 6-Keto-5-methylheptane-*1 : *5-dicarboxylate* (II).—The unsaturated ester (I) (86 g.) was hydrogenated in alcohol in the presence of palladised strontium carbonate (3 g., 12%) until hydrogenation was complete (1 mol.). After removal of catalyst and solvent, the saturated *keto*-diester distilled as a colourless oil, b. p. 118°/0·2 mm., n_D^{20} 1·4479 (Found : C, 61·9; H, 9·2. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%).

7-Keto-5-methyloctanoic Acid (III).—The foregoing ester (69 g.) was refluxed with concentrated hydrochloric acid and water (200 ml. of each) until evolution of carbon dioxide ceased (6 hours). The oil was taken up in benzene, the residue remaining after removal of solvent was refluxed for 2 hours with sodium hydroxide (100 ml.; 5N.), and the solution was steam-distilled. Acidification of the residue furnished an oil which was isolated in the usual manner. *7-Keto-5-methyloctanoic acid* was obtained thereby as a viscous oil (33 g., 75%), b. p. 114°/0·1 mm., n_D^{20} 1·4528 (Found : C, 62·8; H, 9·5%; equiv., 173. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%; equiv., 172). The p-*bromophenacyl* ester, crystallised from aqueous alcohol, had m. p. 60—61° (Found : C, 54·7; H, 5·6. $C_{17}H_{21}O_4Br$ requires C, 55·3; H, 5·7%), and the *semicarbazone* crystallised from ethyl acetate–dioxan in tiny prisms, m. p. 146—147° (Found : N, 17·7. $C_{10}H_{19}O_3N_3$ requires N, 18·3%).

Ethyl 7-Keto-5-methyloctanoate.—A mixture of the acid (55 g.), ethanol (100 ml.), benzene (100 ml.), and sulphuric acid (2 g.) was distilled through a Fenske column fitted with a phase-separator until no further separation took place. The cooled residue was washed with water, sodium hydrogen carbonate solution, and water successively. After removal of solvent, the *ester* was obtained as a colourless oil which distilled at 91—92°/0·5 mm. and had n_D^{20} 1·4362 (62 g., 97%) (Found : C, 65·7; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·1%).

Wolff–Kishner Reduction of (III).—The foregoing keto-acid (10 g.) was reduced with sodium hydroxide (5 g.), hydrazine hydrate (13 ml.; 60%), and 2 : 2′-dihydroxydiethyl ether (75 ml.) in the manner described by Huang-Minlon (*loc. cit.*), and the reduced acid, (±)-*5-methyloctanoic acid*, isolated as an oil (9 g.), b. p. 150°/30 mm., n_D^{20} 1·4355 (Found : C, 68·1; H, 11·5%; equiv., 158. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%; equiv., 158). The *p*-bromophenacyl ester crystallised from aqueous alcohol in colourless plates, m. p. 46—46·5°, undepressed by admixture with the material prepared synthetically.

Synthesis of (±)-*5-Methyloctanoic Acid.*—1-Chloro-5-methylheptene (VI) was prepared as described by Cason *et al.* (*loc. cit.*) for the higher homologue, using *n*-propyl bromide (80 g.), magnesium (16 g.), and 1-chloropentan-4-one (80 g.; freshly distilled). The product boiled at 70—73°/22 mm. and contained about 15% of ketone (oxime value). The crude product (41 g.) was thoroughly shaken with a solution of hydroxylamine hydrochloride (20 g.) in water (100 ml.), sufficient sodium hydroxide solution being added from time to time to keep the aqueous solution alkaline to *p*-bromophenol-blue. When no further alkali was needed, the chloro-compound was extracted with benzene. The organic layer was washed with water, dried ($CaCl_2$), and distilled to give the *chloro-olefin* as a colourless, mobile liquid (36 g.), b. p. 72°/22 mm., n_D^{20} 1·4514, possessing an unpleasant odour (Found : C, 65·5; H, 10·3. $C_8H_{15}Cl$ requires C, 65·5; H, 10·2%).

The above chloro-compound (34 g., 0·23 mol.) was hydrogenated in 95% ethanol in the presence of Adams's catalyst (0·2 g.). Absorption of hydrogen was extremely rapid and finally stopped when a total of 6·3 l. had been absorbed (theory, 5·2 l.). After removal of catalyst by filtration, the filtrate was carefully neutralised with 10N-sodium hydroxide, the amount of the latter being in accord with that required if the excess of hydrogen was used to displace chlorine as hydrogen chloride. A solution of potassium cyanide (32 g.) in water (50 ml.) was then added to the filtrate containing the saturated chloro-compound together with potassium iodide (5 g.) and ethanol (150 ml.), and the mixture digested on the steam-bath for 30 hours. After cooling, the supernatant liquid was decanted from the solid material which was washed with fresh ethanol (50 ml.). Sodium hydroxide (50 ml.; 10N.) was added to the combined alcoholic extracts, and the solution refluxed for a further 30 hours. Water was then added and the mixture steam-distilled to remove a small amount of an evil-smelling material, presumably the *iso*cyanide. Acidification (fume-cupboard) of the residue yielded (±)-5-methyloctanoic acid which was isolated in the usual manner as an oil, b. p. 150°/30 mm., n_D^{20} 1·4355 (Found : C, 68·2; H, 11·5%). The yield of this acid was 24 g. (66% based on chloro-olefin, or 81% if allowance is made for the extra hydrogen consumed during the hydrogenation of the chloro-olefin resulting in the formation of the corresponding paraffin).

The p-*bromophenacyl* ester separated from aqueous alcohol in colourless plates, m. p. 46—46·5° (Found: C, 57·6; H, 6·9. $C_{17}H_{23}O_3Br$ requires C, 57·5; H, 6·5%).

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Birkbeck College, London, E.C.4.

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73. *Isomerisation Reactions. Part III.*

By R. R. Aitken, G. M. Badger, and J. W. Cook.

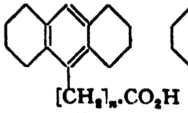
The action of hydrogen fluoride on a series of acids (III; $n = 0, 1, 2, 3$) derived from durene has been investigated. In two cases ($n = 0$ or 1) no reaction occurred. *β-Durylpropionic acid* ($n = 2$) gave a mixture of ketones (IV and V), one formed by elimination of a methyl group and the other by migration. *γ-Durylbutyric acid* ($n = 3$) gave 5 : 6 : 7 : 8-tetramethyl-1-tetralone (VI) by migration of methyl. *β-Pentamethylphenylpropionic acid* reacted with hydrogen fluoride to give (V), with elimination of methyl, whereas *γ-pentamethylphenylbutyric acid* gave no ketonic product.

Compounds of type (I), in which $n = 2$ or 3, undergo isomerisation and cyclisation on treatment with anhydrous hydrogen fluoride at room temperature, to give derivatives of *s*-octahydrophenanthrene (II) (Badger, Carruthers, Cook, and Schoental, *J.*, 1949, 169; Badger, Carruthers, and Cook, *ibid.*, p. 2044). Cyclisation is evidently essential for isomerisation to occur, for hydrogen fluoride did not isomerise a number of related compounds in which the subsequent cyclisation could not take place. The analogy between this type of isomerisation and that observed with aluminium chloride has already been noted, as well as the analogy to the Jacobsen reaction, in which isomerisations are brought about by concentrated sulphuric acid. In these last two cases, however, cyclisation is not an essential feature, and in this respect, therefore, the isomerisations observed with hydrogen fluoride, at room temperature, appear to be unique. However, the displacement of an alkyl group by an entering acyl group in the preparation of aromatic ketones using aluminium chloride has been reported by Auwers and Mauss (*Annalen*, 1928, **460**, 240), and by Hennion and McLeese (*J. Amer. Chem. Soc.*, 1942, **64**, 2421).

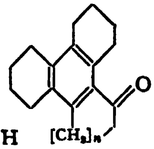
Baddeley (*J.*, 1944, 232) has pointed out that migrations of alkyl groups in benzene homologues, phenols, aryl ketones, and hydroxyaryl ketones by means of aluminium chloride are related to one another and to the Jacobsen reaction. He also distinguishes between two types of aluminium chloride isomerisations, namely (i) the reversible isomerisation of homologues of benzene and phenol associated with intramolecular migrations of alkyl groups to adjacent positions, and (ii) the irreversible isomerisation of aromatic ketones, closely comparable with the Jacobsen reaction, which involve intramolecular migration of alkyl groups to adjacent positions and, alternatively, migration, perhaps intramolecular, of acyl groups. The hydrogen fluoride rearrangements of octahydroanthracene derivatives show some of the features of both types. For this reason, and because most of the work on the Jacobsen reaction has been carried out with polyalkylbenzenes ("Organic Reactions," 1942, Vol. I, p. 370), we have extended our studies with hydrogen fluoride to some derivatives of durene and of pentamethylbenzene.

Durene itself was unaffected by hydrogen fluoride at room temperature, a result which is in agreement with previous work (Calcott, Tinker, and Weinmayr, *J. Amer. Chem. Soc.*, 1939, **61**, 1010), although it is known that hydrogen fluoride isomerises homologues of benzene at high temperatures and pressures (U.S.P. 2,416,184).

Similarly, durenecarboxylic acid and *durylacetic acid* (III; $n = 1$) were recovered unchanged after treatment with hydrogen fluoride, and in this respect, these results are entirely comparable with those observed in the case of octahydroanthracene and its simple derivatives (Badger, Carruthers, and Cook, *loc. cit.*). With β-*durylpropionic acid* (III; $n = 2$), and with *γ-durylbutyric acid* (III; $n = 3$), cyclisation and isomerisation were observed.



(I.)



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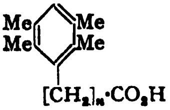

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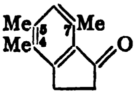

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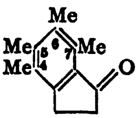

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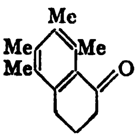

(VI.)

Treatment of β-durylpropionic acid with hydrogen fluoride gave a mixture from which 4 : 5 : 7-*trimethylindan*-1-*one* (IV) and 4 : 5 : 6 : 7-*tetramethylindan*-1-*one* (V) were isolated and characterised as the *oximes*. The former ketone is formed by simultaneous cyclisation with the *loss* of a methyl group, and the latter, formed in rather greater amount, by simultaneous cyclisation with *migration* of a methyl group. Similar effects have often been observed in isomerisations with other reagents such as aluminium chloride. The structures of the two ketones were established by oxidation with dilute nitric acid to the corresponding benzene-polycarboxylic acids. Cyclisation and isomerisation of γ-durylbutyric acid proceeded rather more readily, and in better yield, to give only one ketone. This ketone, also characterised as its *oxime*, was oxidised to mellitic acid, and was therefore 5 : 6 : 7 : 8-*tetramethyl*-1-*tetralone* (VI).

β-*Pentamethylphenylpropionic acid* on treatment with hydrogen fluoride gave only one ketone, namely 4 : 5 : 6 : 7-tetramethylindanone (V), formed by cyclisation with elimination of a methyl group. Unexpectedly, the homologous acid, γ-*pentamethylphenylbutyric acid* gave no ketonic product with hydrogen fluoride.

Durenecarboxylic acid was prepared from bromodurene by carboxylation of its magnesio-derivative (Fuson and Kelton, *J. Amer. Chem. Soc.*, 1941, **63**, 1500). Chloromethylation of durene, by a modification of the method used by Nauta and Dienske (*Rec. Trav. chim.*, 1936, **55**, 1000) for mesitylene, gave chloromethyldurene and *bischloromethyldurene*. The former, on interaction with potassium cyanide, followed by hydrolysis of the resulting *cyanomethyldurene*, gave durylacetic acid (III; $n = 1$). Condensation of chloromethyldurene with ethyl sodiomalonate gave *ethyl durylmethylmalonate*, which on hydrolysis to the *acid* followed by decarboxylation gave β-durylpropionic acid (III; $n = 2$). Chain lengthening by the Arndt–Eistert procedure gave, through the *amide*, γ-durylbutyric acid (III; $n = 3$). β-Pentamethylphenylpropionic acid and γ-pentamethylphenylbutyric acid were obtained from pentamethylbenzene by exactly similar routes. The former was also prepared by chloromethylation of β-durylpropionic acid followed by catalytic hydrogenation of the *chloromethyldurylpropionic acid* so formed.

The Friedel–Crafts reaction between durene and succinic anhydride in presence of aluminium chloride has also been investigated. In carbon disulphide solution this gave a mixture from which the normal product, γ-*keto*-γ-*durylbutyric acid*, m. p. 160°, was isolated with difficulty, together with the isomeric γ-*keto*-γ-*prehnitylbutyric acid*, m. p. 107°. Under these conditions Muhr (*Ber.*, 1895, **28**, 3217) claimed to have prepared γ-keto-γ-durylbutyric acid, m. p. 117°. This was evidently a mixture. When the reaction was carried out in tetrachloroethane solution γ-keto-γ-durylbutyric acid was more readily obtained pure, its isomer being formed in only small amount. This solvent influence is somewhat similar to that observed by Badger, Carruthers, and Cook (*loc. cit.*) in the corresponding reaction of *s*-octahydroanthracene and succinic anhydride. These authors found that in tetrachloroethane a mixture of keto-acids was formed, whereas the use of carbon disulphide led to more complete isomerisation to octahydrophenanthroylpropionic acid.

Reduction of γ-keto-γ-durylbutyric acid to γ-durylbutyric acid (III; $n = 3$) was difficult, presumably on account of steric hindrance. It was not effected by hydrazine hydrate at 195°, and although the Clemmensen method yielded a small amount of the desired acid much of the keto-acid was unchanged.

EXPERIMENTAL.

Durene.—Durene was prepared by bischloromethylation of technical xylene, followed by reduction of the bischloromethyl compound with zinc and sodium hydroxide solution (von Braun and Nelles, *Ber.*, 1934, **67**, 1094). Reduction by catalytic hydrogenation in acetone, over palladised asbestos, gave a theoretical yield in small-scale (2-g.) runs, but on a large scale the reduction was tediously long and tended to give incompletely reduced material. Durene was recovered unchanged after treatment, for 36 hours, with anhydrous hydrogen fluoride at room temperature.

Chloromethyldurene.—A mixture of durene (22 g.), glacial acetic acid (50 c.c.), concentrated hydrochloric acid (110 c.c.), and aqueous formaldehyde (40%; 10·7 g.) was heated at 70°, for 6 hours, a further quantity (4·4 g.) of formaldehyde being added after 3 hours. After cooling, the aqueous layer was decanted, and the solid dissolved in benzene, washed with sodium carbonate solution and then water, and dried (K_2CO_3). Distillation gave chloromethyldurene (22 g.), b. p. 139—141°/15 mm., which, after crystallisation from methanol, had m. p. 65—66° (Fuson and Sperati, *J. Amer. Chem. Soc.*, 1941, **63**, 2643, give m. p. 67—68°). The solid residue from the distillation was sublimed at 160°/15 mm. Recrystallisation of the sublimate (3—5 g. in different runs) from light petroleum gave *bischloromethyldurene* as colourless needles, m. p. 193—194° (Found: C, 62·0; H, 6·8; Cl, 30·5. $C_{12}H_{16}Cl_2$ requires C, 62·3; H, 7·0; Cl, 30·7%).

Ethyl β-Durylmethylmalonate.—A mixture of atomised sodium (3·5 g.), ethyl malonate (24·2 g.), and benzene (75 c.c.) was heated under reflux for 3 hours. While still warm, chloromethyldurene (25·2 g.) in benzene (40 c.c.) was added, and the whole heated under reflux for a further 2 hours. After cooling, the mixture was poured into water, and the benzene layer separated, washed, and dried. Fractional distillation gave chloromethyldurene, ethyl malonate, and *ethyl β-durylmethylmalonate*, b. p. 158—160°/0·5 mm. (31 g.), which crystallised from light petroleum in colourless prisms, m. p. 58—59° (Found : C, 70·5; H, 8·6. $C_{18}H_{26}O_4$ requires C, 70·6; H, 8·6%). Hydrolysis with aqueous-ethanolic potassium hydroxide for 3 hours gave *β-durylmethylmalonic acid*, which crystallised from water as colourless plates, m. p. 176° (with evolution of carbon dioxide) (Found : C, 67·4; H, 6·9. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

β-Durylpropionic Acid (III; *n* = 2).—The above malonic acid (2 g.) was heated in an oil-bath at 180°, until evolution of gas ceased. *β-Durylpropionic acid* (1·5 g.) formed needles, m. p. 170°, from benzene or aqueous acetic acid (Found : C, 75·6; H, 8·6. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%). *β-Durylpropionamide* crystallised from ethanol in needles, m. p. 201—202° (Found : C, 76·2; H, 9·0; N, 7·0. $C_{13}H_{19}ON$ requires C, 76·1; H, 9·3; N, 6·8%).

Isomerisation and Cyclisation of β-Durylpropionic Acid.—The above acid (2 g.) was allowed to stand with excess of anhydrous hydrogen fluoride for 36 hours. The resulting dark residue was poured on ice and extracted with ether. Extraction of the ethereal solution with dilute sodium carbonate solution, followed by acidification of the extract, gave unchanged acid (1·4 g.) identified by m. p. and mixed m. p. The ethereal solution yielded a brown oil (0·5 g.), which solidified when kept. After purification by passage of its solution in benzene through a column of alumina, the product was obtained as a pale yellow solid which separated from light petroleum as a mixture of ketone-A (needles) and ketone-B (prisms), which were separated mechanically.

Purification of ketone-A by recrystallisation from light petroleum, gave 4 : 5 : 7-*trimethylindan*-1-*one* (IV) as colourless needles, m. p. 104—105° [Found : C, 82·5; H, 8·1%; *M* (Rast), 199. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%; *M*, 174]. The *oxime* formed colourless plates, m. p. 223—224° (decomp.), from benzene–light petroleum (Found : C, 76·3; H, 7·8; N, 7·35. $C_{12}H_{15}ON$ requires C, 76·1; H, 8·0; N, 7·4%). Hydrolysis of the oxime with dilute hydrochloric acid in boiling ethanol regenerated the ketone, of unchanged m. p. For oxidation, the ketone (0·12 g.) was heated at 175—180° in a sealed tube, for 6 hours, with water (2 c.c.) and concentrated nitric acid (1 c.c.). Evaporation to dryness and esterification of the residue with excess of ethereal diazomethane gave methyl benzenepentacarboxylate, m. p. 145—146°, not depressed on admixture with an authentic specimen prepared in a similar manner by oxidation of pentamethylbenzene (*cf.* Cook and Hewett, *J.*, 1934, 371; Fieser and Joshel, *J. Amer. Chem. Soc.*, 1940, **62**, 1213).

Purification of ketone-B by recrystallisation from light petroleum (charcoal) gave 4 : 5 : 6 : 7-*tetramethylindan*-1-*one* (V) as colourless plates, m. p. 149—150° [Found : C, 82·8; H, 8·6%; *M* (Rast), 172. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6%; *M*, 188]. The m. p. was unchanged when the ketone was purified through its *oxime*, which crystallised from ethanol in small needles, m. p. 211—213° (Found : C, 77·0; H, 8·4; N, 7·2. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4; N, 6·9%). Oxidation of tetramethylindanone with dilute nitric acid, as described above for trimethylindanone, gave methyl mellitate, m. p. 186—187°, from methanol, not depressed by admixture with an authentic specimen, m. p. 187—188°.

γ-Keto-γ-duryl- and γ-Keto-γ-prehnityl-butyric Acid.—To a stirred ice-cold suspension of aluminium chloride (10 g.) in carbon disulphide (30 c.c.), a solution of durene (3·3 g.) and succinic anhydride (2·5 g.) in carbon disulphide (50 c.c.) was added dropwise, during 30 minutes. After being stirred for 4 hours at 0° and then 8 hours at room temperature, the mixture was set aside, without stirring, for a further 16 hours. The acidic product (3·2 g.) had m. p. 117—134°, and was purified by crystallisation from ethanol, followed by crystallisation of the sodium salt from water. *γ-Keto-γ-durylbutyric acid*, obtained from the purified sodium salt, formed colourless prisms, m. p. 160—161°, from ethanol (Found : C, 71·5; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Durene was regenerated when this acid was heated with concentrated hydrochloric acid in a sealed tube at 150° for 6 hours. The p-*nitrobenzyl* ester crystallised from methanol in plates, m. p. 120—121° (Found : C, 68·3; H, 6·4; N, 3·5. $C_{21}H_{23}O_5N$ requires C, 68·3; H, 6·3; N, 3·8%).

The same acid was isolated following interaction of durene and succinic anhydride with aluminium chloride, in tetrachloroethane solution.

The acid recovered from the mother-liquors of the sodium salt was crystallised from aqueous ethanol and then benzene–hexane, and gave *γ-keto-γ-prehnitylbutyric acid*, m. p. 107—108° (Found : C, 71·6; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). This acid (0·1 g.) was added to ice-cold 10% sodium hypobromite solution (10 c.c.), and the suspension gradually heated to 100°, with occasional shaking (2 hours). The mixture was maintained at 100° for 3 hours and filtered hot. Acidification gave prehnitenecarboxylic acid, m. p. 165—166°, from ligroin (lit., m. p. 168—169°), and the amide prepared from it had m. p. 220° (lit., m. p. 222°).

γ-Durylbutyric Acid (III; *n* = 3).—(*a*) A mixture of β-durylpropionic acid (III; *n* = 2) (2 g.), thionyl chloride (2·5 c.c.), benzene (15 c.c.), and pyridine (1 drop) was refluxed for 2 hours. The benzene and excess of thionyl chloride were then removed in a vacuum, and the residue was evaporated with two portions (10 c.c. each) of benzene. The residue was then dissolved in benzene (20 c.c.) and added gradually, with stirring, to an ice-cold solution of diazomethane (from 7 g. of nitrosomethylurea) in ether (120 c.c.). The resulting solution was evaporated to dryness in a stream of dry air, and the residue, in dioxan (20 c.c.), was refluxed for 2½ hours with a solution of 10% silver nitrate (3 c.c.) and 20% ammonia (15 c.c.). The resulting mixture was filtered hot, the residue on the paper was washed with hot dioxan, and the combined solutions were poured into water. *γ-Durylbutyramide* (1·05 g.) crystallised from ethanol in colourless plates, m. p. 171—172° (Found : C, 76·8; H, 9·5; N, 6·1. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·7; N, 6·4%). Hydrolysis of the amide (1 g.) was effected by 10 hours' refluxing with potassium hydroxide (5 g.) in ethanol (50 c.c.). *γ-Durylbutyric acid* (III; *n* = 3) (0·89 g.) crystallised from benzene, and then from *cyclo*hexane, in colourless plates, m. p. 139—140° (Found : C, 76·2; H, 9·0. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%).

(*b*) An attempt to prepare durylbutyric acid by reduction of γ-keto-γ-durylbutyric acid by the modified Kishner–Wolff procedure (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) was unsuccessful, only unchanged material being isolated. Reduction by the Clemmensen method was, however, partly successful. A mixture of γ-keto-γ-durylbutyric acid (1·5 g.), toluene (15 c.c.), acetic acid (10 c.c.), concentrated hydrochloric acid (75 c.c.), and amalgamated zinc (10 g.) was refluxed for 48 hours. Additions of zinc (total, 15 g.) and of hydrochloric acid (total, 75 c.c.) were made at intervals. The product, m. p. 114—130°, was purified by conversion into the sodium salt, and separation into soluble and sparingly soluble fractions. Acidification of the sparingly soluble salt gave unchanged keto-acid (1·0 g.), identified by m. p. and mixed m. p. Acidification of the soluble salt, followed by recrystallisation of the product from *cyclo*hexane, gave γ-durylbutyric acid (0·27 g.), m. p. 138—139°, identical with that obtained as under (*a*).

Isomerisation and Cyclisation of γ-Durylbutyric Acid (III; *n* = 3).—γ-Durylbutyric acid (1 g.) was set aside in excess of anhydrous hydrogen fluoride for 36 hours. The resulting brown residue was poured on ice and extracted with ether. Extraction of the ethereal solution with dilute sodium carbonate solution, followed by acidification of the extract, gave unchanged acid (0·38 g.), identified by m. p. and mixed m. p. Evaporation of the ethereal solution gave a slightly coloured solid residue which on crystallisation from ethanol (twice) gave 5 : 6 : 7 : 8-*tetramethyl*-1-*tetralone* (VI) as colourless needles, m. p. 106—107° [Found: C, 83·4; H, 9·2%; *M* (Rast), 200. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%; *M*, 202]. The *oxime* formed colourless needles, m. p. 185—186°, from ethanol (Found: C, 77·15; H, 8·8; N, 6·6. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8; N, 6·45%). The oxime (0·05 g.), hydrolysed as described above for trimethylindanone, yielded after crystallisation from ethanol the ketone of the same m. p. Oxidation of this ketone (VI) with dilute nitric acid as described above for trimethylindanone yielded methyl mellitate, m. p. 185—187°, from methanol, not depressed on admixture with an authentic specimen.

Durenecarboxylic Acid.—This was obtained from the bromo-derivative by interaction with magnesium in dry ether, followed by carboxylation with solid carbon dioxide. It crystallised from light petroleum in colourless plates, m. p. 178°. Fuson and Kelton (*J. Amer. Chem. Soc.*, 1941, **63**, 1500) give m. p. 179—180°. It was recovered unchanged after being kept in anhydrous hydrogen fluoride, at room temperature, for 48 hours.

Durylacetic Acid.—Potassium cyanide (5 g.) in water (9 c.c.) was added to chloromethyldurene (2 g.) in ethanol (25 c.c.), and the mixture was boiled under reflux for 2 hours. The cooled solution was added to a large excess of water. The precipitated *cyanomethyldurene* formed needles, m. p. 84—85° (from aqueous methanol), after distillation (b. p. 168°/20 mm.) (Found: C, 83·3; H, 8·5; N, 8·3. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1%). Hydrolysis of the crude cyanide, by boiling with a mixture of equal volumes of sulphuric acid, water, and acetic acid, gave *durylacetic acid* which crystallised from benzene in colourless plates, m. p. 198—199° (Found: C, 75·2; H, 8·1. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). Durylacetic acid was recovered unchanged after treatment with hydrogen fluoride, at room temperature, for 48 hours.

Pentamethylbenzene.—Pentamethylbenzene was prepared by bischloromethylation of mesitylene (Nauta and Dienske, *Rec. Trav. chim.*, 1936, **55**, 1000), followed by reduction of the bischloromethyl compound. Several methods were investigated in an attempt to accomplish this reaction. Reduction by catalytic hydrogenation with palladised asbestos in acetone, though efficient in small scale runs (2 g.) as with dichloromethylxylene, was found to be tediously long and to give incompletely reduced products. Reduction with zinc and aqueous alcohol (*cf.* Hewett, *J.*, 1940, 298) gave mainly non-crystalline undistillable products, as did reduction with nickel–aluminium alloy and aqueous sodium hydroxide, at about 90°. The reduction was most readily accomplished by stirring the bischloromethylmesitylene, in toluene, with zinc and aqueous sodium hydroxide. When benzene was used in place of toluene, as described by von Braun and Nelles (*Ber.*, 1934, **67**, 1094) for the reduction of bischloromethylxylene, the yield of pentamethylbenzene was considerably reduced.

Pentamethylbenzene was also obtained by shaking chloromethyldurene (10 g.) in acetone (150 c.c.) with hydrogen at ordinary pressures and temperatures in presence of palladium on asbestos as catalyst. Reduction was complete within 3¾ hours.

Pentamethylchloromethylbenzene.—A mixture of pentamethylbenzene (14 g.), concentrated hydrochloric acid (70 c.c.), and aqueous formaldehyde (7 g.; 40%) was stirred while being heated at 65° for 6 hours, a further quantity (2·5 g.) of formaldehyde being added after 3 hours. After cooling, the aqueous layer was decanted and the semi-solid residue dissolved in benzene, washed with sodium carbonate solution and then with water, and dried (K_2CO_3). Distillation yielded *pentamethylchloromethylbenzene* (12 g.), b. p. 148°/14 mm., which crystallised from light petroleum in prisms, m. p. 82—84° (Found: C, 73·05; H, 8·8; Cl, 17·9. $C_{12}H_{17}Cl$ requires C, 73·3; H, 8·7; Cl, 18·0%). Pentamethylchloromethylbenzene was also obtained, though mixed with hexamethylbenzene, by treating hexamethylbenzene with phosphorus pentachloride as described by Jacobsen (*Ber.*, 1889, **22**, 1217), who claims to have obtained pentamethylchloromethylbenzene, m. p. 99°, by this method.

Ethyl Pentamethylbenzylmalonate.—A mixture of atomised sodium (1·7 g.), ethyl malonate (11·6 g.), and benzene (50 c.c.) was heated under reflux for 3 hours. Whilst still warm, pentamethylchloromethylbenzene (12 g.) in benzene (20 c.c.) was added, and the whole heated under reflux for a further 2 hours. The cooled mixture was then poured into water, and the benzene layer separated, washed, and dried. Distillation gave *ethyl pentamethylbenzylmalonate*, b. p. 177—180°/1·5 mm. (14·5 g.), which crystallised from ethanol in needles, m. p. 71—73° (Found: C, 71·2; H, 8·9. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%). Hydrolysis of the ester (14·5 g.) with aqueous-ethanolic potassium hydroxide for 2 hours gave *pentamethylbenzylmalonic acid* (9·4 g.), which formed plates, m. p. 191·5° (with evolution of carbon dioxide), from aqueous ethanol (3 : 1) (Found: C, 68·45; H, 7·8. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

β-Pentamethylphenylpropionic Acid.—The malonic acid (9·4 g.) was heated in an oil-bath at 195° till evolution of gas had ceased. *β-Pentamethylphenylpropionic acid* (6·4 g.) formed needles, m. p. 175—176°, from benzene (Found: C, 76·2; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

This acid was also obtained as follows. A mixture of β-durylpropionic acid (2 g.), aqueous formaldehyde (1·5 g.; 40%), and concentrated hydrochloric acid (20 c.c.) was stirred for 6 hours whilst being heated at 60°. After 3 hours a further quantity (1·0 g.) of formaldehyde was added. The cooled mixture was added to water and filtered. *β-Chloromethyldurylpropionic acid* formed needles, m. p. 216—218°, from dioxan (Found: C, 66·2; H, 7·45; Cl, 14·1. $C_{14}H_{19}O_2Cl$ requires C, 66·0; H, 7·5; Cl, 13·9%).

β-Acetoxymethyldurylpropionic acid, prepared from this by warming it with sodium acetate in acetic acid to 100° for 30 minutes, formed long fine needles, m. p. 203—204°, from aqueous acetic acid (Found : C, 69·0; H, 8·0. $C_{16}H_{22}O_4$ requires C, 69·0; H, 8·0%). *β-Hydroxymethyldurylpropionic acid*, prepared by sodium carbonate hydrolysis of either of the above two acids, formed large firm needles, m. p. 213—214° with evolution of gas (from ethyl acetate) (Found : C, 71·4; H, 8·4. $C_{14}H_{20}O_3$ requires C, 71·15; H, 8·5%).

One run of the chloromethylation reaction, when acetic acid was present, yielded β-acetoxymethyldurylpropionic acid; its identity was shown by m. p. and mixed m. p. with a specimen prepared as described above and by hydrolysis with sodium carbonate to β-hydroxymethyldurylpropionic acid.

Chloromethyldurylpropionic acid (0·3 g.) in acetone (15 c.c.) was shaken with hydrogen at ordinary temperature and pressure in presence of palladium-black. Reduction was complete in 2 hours. The filtered residue yielded β-pentamethylphenylpropionic acid, m. p. 172—174°, not depressed by mixture with the specimen prepared as described above.

Isomerisation and Cyclisation of β-Pentamethylphenylpropionic Acid.—The acid (1 g.) was left in contact with excess of anhydrous hydrogen fluoride for 36 hours. The resulting brown oil was poured on ice and extracted with ether. Extraction of the ethereal solution with sodium carbonate solution followed by acidification of the alkaline extract gave unchanged acid (0·37 g.). The ethereal solution yielded a brown oil (0·54 g.) which solidified in an ice-bath. After purification by passage of its benzene solution through a column of alumina the product, a pale yellow solid, was crystallised from light petroleum. It formed plates, m. p. 150—152°, not depressed by admixture with tetramethylindanone (V). Identification was completed by preparation of the oxime, m. p. 213—214°.

γ-Pentamethylphenylbutyric Acid.—A mixture of β-pentamethylphenylpropionic acid (2·2 g.), thionyl chloride (2·75 c.c.), benzene (15 c.c.), and pyridine (1 drop) was refluxed for 2 hours. The benzene and excess of thionyl chloride were removed *in vacuo*, and the residue was evaporated with 2 portions (10 c.c. each) of dry benzene. The residue in benzene (20 c.c.) was added with stirring to an ice-cold solution of diazomethane (from 8 g. of nitrosomethylurea) in ether (150 c.c.). The resulting mixture, from which part of the diazoketone could be crystallised by cooling it in ice, was evaporated to dryness in a stream of dry air, and the residue, dissolved in dioxan (25 c.c.), was refluxed for 2½ hours with a solution of silver nitrate (3 c.c.; 10%) and ammonia (15 c.c.; 20%). The resulting mixture was filtered hot, the residue on the paper was washed with hot ethanol, and the combined solutions were poured into water. *γ-Pentamethylphenylbutyramide* (1·15 g.) formed very small needles, m. p. 185—186°, from benzene (Found : C, 77·4; H, 10·2; N, 6·4. $C_{15}H_{23}ON$ requires C, 77·2; H, 9·9; N, 6·0%). Hydrolysis of the amide (1·15 g.) was effected by refluxing it for 10 hours with potassium hydroxide (5 g.) in ethanol (50 c.c.). *γ-Pentamethylphenylbutyric acid* (0·75 g.) formed plates, m. p. 157—158°, from benzene (Found : C, 76·8; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%). When this acid was left in contact with excess of hydrogen fluoride for 36 hours it was recovered entirely unchanged.

One of us (G. M. B.) has held an I.C.I. Research Fellowship during this investigation. We are also indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance (to R. R. A.). Microanalyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, October 26th, 1949.*]

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74. *Acetylene Reactions. Part VII. Acetylenic Amino-alcohols from Benzophenones.*

By H. P. W. HUGGILL and J. D. ROSE.

Compounds of the type $CPh_2(OH)\cdot C\vdots C\cdot CHR\cdot NR'_2$ and their semi- and completely hydrogenated analogues have been prepared for test as spasmolytics. Two methods have been used : (*a*) when R = CH_3, by interaction of 3-alkylamino- and 3-dialkylamino-but-1-ynes with benzophenones; and (*b*), when R = H, from diphenylethynylcarbinol or its acetate, formaldehyde, and a secondary amine. Some reactions of these compounds, particularly their hydrogenation, addition of hydrogen chloride, and Meyer–Schuster rearrangement with sulphuric acid, are described.

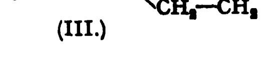
As part of a general programme of work on spasmolytic substances, unsaturated derivatives of diphenylcarbinol were required containing a basic substituent in the unsaturated side chain. Substances of type (I) and their ethylenic analogues, which have some structural similarity to " Trasentin " (II) (Meier and Salow, *Klin. Wochenschr.*, 1936, 15, 1403, 1405), " Aspasin " (III) (B.I.O.S. Final Report No. 116, p. 57), and the 3-dialkylamino-1 : 1-diphenylpropanols (IV) (Roche Products Ltd., B.P. 615,136), seemed to be most readily accessible.

$CPh_2(OH)\cdot C\vdots C\cdot CHR\cdot NR'_2$

(I.)

$CHPh_2\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NEt_2$

(II.)



(III.)

$CPh_2(OH)\cdot CH_2\cdot CH_2\cdot NR_2$

(IV.)

Two routes were used for the preparation of these compounds. The first was based on the availability of the 3-alkylamino- and 3-dialkylamino-but-1-ynes (Part I of this series, *J.*, 1949, 780) which condensed readily with benzophenone in the presence of alkali to give the required acetylenic amino-alcohols. This reaction was not completely general, and failed with 4 : 4′-bisdimethylaminobenzophenone (Michler's ketone).

The second route involved the Mannich reaction of diphenylethynylcarbinol (from benzophenone and acetylene), formaldehyde, and the secondary amine. In this reaction it was found advantageous to acetylate the carbinol before carrying out the Mannich condensation, as otherwise very low yields were obtained. It is noteworthy that during the Mannich condensation the acetyl group was lost and the resulting amino-acetylenic alcohols could not subsequently be reacetylated. This failure is not unexpected, since not only is the hydroxyl group tertiary, but the molecule contains in addition a strongly basic group and is too unstable to acid reagents to permit very drastic acetylation conditions.

The loss of the acetyl group during the Mannich reaction is more surprising. Judged by the difference in reactivity between the carbinol and its acetate in this reaction, it would appear that deacetylation does not precede the Mannich reaction, and the use of morpholine hydrochloride in place of the free base did not prevent deacetylation. The higher yield obtained from the acetate than from the carbinol is in accord with the findings of Jones, Marszak, and Bader (*J.*, 1947, 1578).

The acetylenic amino-alcohols underwent catalytic reduction to either the ethylenic or the saturated analogues, although there was considerable variation in the ease of reduction beyond the ethylenic stage. Those alcohols derived from the 3-dialkylamino- and 3-alkylamino-but-1-ynes (I; R = Me) tended to split off the amino-group in the second stage of the reduction, and attempted saturation of 4-morpholino-1 : 1-diphenylpent-2-yn-1-ol caused complete disruption of the molecule. Amines of the type (I; R = H) were easier to reduce and the reduction products were stable.

With sulphuric acid the 4-dialkylamino-1 : 1-diphenylpent-2-yn-1-ols underwent the Meyer–Schuster rearrangement to 4-dialkyamino-1 : 1-diphenylpent-1-en-3-ones (V), but with hydrochloric acid simple adducts (VI) of the acetylenic amines with HCl were obtained which on treatment with alkali regenerated the original amine and with sulphuric acid gave the αβ-unsaturated ketones.

$$\begin{tikzcd}[column sep=large]
\text{(I)} \arrow[r, shift right, "\text{NaOH}"'] \arrow[rr, bend right=25, "\text{H}_2\text{SO}_4"'] & \underset{\text{(VI.)}}{\text{CPh}_2\text{(OH)}\cdot\text{CH:CCl}\cdot\text{CHR}\cdot\text{NR}'_2} \arrow[l, shift right, "\text{HCl}"'] \arrow[r, "\text{H}_2\text{SO}_4"] & \underset{\text{(V.)}}{\text{CPh}_2\text{:CH}\cdot\text{CO}\cdot\text{CHR}\cdot\text{NR}'_2}
\end{tikzcd}$$

The fact that (I) is regenerated by alkali treatment of (VI) disposes of the possibility that the hydrogen chloride adducts might be those of the αβ-unsaturated ketone (V), and the conversion of (VI) into (V) by dilute sulphuric acid considerably strengthens the probability that the orientation of the adduct is as shown. The addition of hydrogen chloride to acetylenic amines does not appear to have been recorded previously, although there are a few examples of its addition to acetylenic carbinols (see Johnson, "The Chemistry of the Acetylenic Compounds," Vol. I, p. 101, Arnold, 1946); in most of these cases dehydration to a vinylacetylene was possible and may have preceded addition. Where simple addition occurred, the position of the halogen was not determined.

EXPERIMENTAL.

The 3-alkylamino- and 3-dialkylamino-but-1-ynes used in this work were prepared by the methods of Part I of this series (*loc. cit.*).

*4-Dimethylamino-*1 : 1-*diphenylpent*-2-*yn*-1-*ol.*—A solution of benzophenone (175 g.) and 3-diethylaminobut-1-yne (105 g.) in ether (200 c.c.) was added during one hour to a stirred suspension of powdered potassium hydroxide (180 g.) in dry ether (700 c.c.) at 15—20°. After 16 hours' stirring, water (1 l.) was added, and the mixture filtered, giving 97 g. of crude amine (32% based on the dimethylaminobutyne). The ethereal layer from the filtrate was shaken with 1·5N-hydrochloric acid (1 l.) which gave, after filtration, 80 g. (24%) of the base hydrochloride. From the filtrates 49 g. of benzophenone and 36 g. of unchanged 3-dimethylaminobut-1-yne were recovered. When crystallised from methyl alcohol, *4-dimethylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol* formed white plates, m. p. 144—146° (Found: C, 82·1; H, 7·2; N, 5·3. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%). The *methiodide* formed white plates (from methyl alcohol), m. p. 223° (decomp.; bath pre-heated to 205°) (Found: C, 57·0; H, 5·8; N, 3·3. $C_{20}H_{24}ONI$ requires C, 57·0; H, 5·7; N, 3·3%). The *hydrochloride*, white needles from aqueous alcohol, had m. p. 189° (decomp.; bath pre-heated to 180°) (Found: C, 66·8; 66·8; H, 6·8; 7·3; N, 4·25. $C_{19}H_{21}ON,HCl,1{\cdot}5H_2O$ requires C, 66·6; H, 7·3; N, 4·1%). Attempts to form the acetate with acetyl chloride in pyridine were unsuccessful.

4-*Morpholino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*.—3-Morpholinobut-1-yne (21 g.) and benzophenone (27·2 g.) were brought into reaction with potassium hydroxide powder (27 g.) in ether (120 c.c.) as described above for the dimethylamino-analogue. The *amino-alcohol* (17 g., 35%) was obtained as white plates, m. p. 142—144°, from methyl alcohol (Found : C, 78·6; H, 7·1; N, 4·55. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·1; N, 4·35%). The *methiodide* formed white needles, m. p. 202—203° (decomp.), from methyl alcohol (Found : C, 56·6; H, 5·8; N, 3·0. $C_{22}H_{26}O_2NI$ requires C, 57·0; H, 5·6; N, 3·0%). The *hydrochloride* formed white plates, m. p. 186° (decomp.; bath preheated to 175°), from methyl alcohol (Found : C, 67·2; H, 6·9; N, 3·6. $C_{21}H_{23}O_2N,HCl,H_2O$ requires C, 67·2; H, 6·9; N, 3·7%). No acetyl derivative could be prepared.

4-*Diethylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*.—A solution of benzophenone (180 g.) and 3-diethylaminobut-1-yne (120 g.) in ether (250 c.c.) was added during one hour to a stirred suspension of powdered potassium hydroxide (180 g.) in dry ether (750 c.c.) at 15—20°. After 16 hours' stirring, water (1 l.) was added, and the ethereal layer separated and extracted with water (1 l.) containing concentrated hydrochloric acid (150 c.c.). The aqueous layer was made strongly alkaline with 10N-sodium hydroxide and extracted with ether. Distillation of the dried ethereal solution gave 53 g. (44%) of unchanged diethylaminobutyne and a residue (135 g.) of 4-*diethylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*, which after crystallisation from light petroleum (b. p. 60—80°) formed white prisms m. p. 81—82° (Found : C, 81·7; H, 7·8; N, 4·35. $C_{21}H_{25}ON$ requires C, 82·1; H, 8·1; N, 4·55%). The *methiodide* formed white needles, m. p. 183°, from water (Found : C, 58·6; H, 5·75; N, 3·0. $C_{22}H_{28}ONI$ requires C, 58·9; H, 6·24; N, 3·1%). The *hydrochloride* formed white needles, m. p. 178° (decomp.), from dioxan (Found : N, 3·9. $C_{21}H_{25}ON,HCl$ requires N, 4·0%). No acetyl derivative could be obtained.

4-*Diethylamino*-1 : 1-*di*-p-*tolylpent*-2-*yn*-1-*ol*.—Di-*p*-tolyl ketone (5 g.), 3-diethylaminobut-1-yne (5 g.), and powdered potassium hydroxide (5 g.) were caused to interact as above in ether (50 c.c.) for 48 hours to give the *amino-alcohol* (2·0 g.) as white prisms, m. p. 85°, from light petroleum (b. p. 60—80°) (Found : C, 82·1; H, 8·35; N, 3·7. $C_{23}H_{29}ON$ requires C, 82·4; H, 8·7; N, 4·2%). The *methiodide* formed white prisms (from ethyl alcohol), m. p. 183—185° (decomp.) (Found : C, 60·6; H, 6·8; N, 2·7. $C_{24}H_{32}ONI$ requires C, 60·4; H, 6·7; N, 2·9%).

4-*Diethylamino*-1-*phenyl*-1-p-*tolylpent*-2-*yn*-1-*ol*.—This was prepared from 3-diethylaminobut-1-yne (16 g.), phenyl *p*-tolyl ketone (25 g.), and powdered potassium hydroxide in the usual manner. The *amino-alcohol* formed white prisms, m. p. 66—67°, from light petroleum (b. p. 60—80°) (Found : C, 82·2; H, 8·3; N, 4·2. $C_{22}H_{27}ON$ requires C, 82·2; H, 8·4; N, 4·4%). The *methiodide* formed white prisms (from alcohol), m. p. 212—214° (decomp.; bath preheated to 205°) (Found : C, 59·1; H, 6·5. $C_{23}H_{30}ONI$ requires C, 59·5; H, 6·5%). The *hydrochloride* formed white needles, m. p. 175° (decomp., bath preheated to 165°), from water (Found : C, 72·5; H, 7·8. $C_{22}H_{27}ON,HCl,0{\cdot}5H_2O$ requires C, 72·05; H, 7·8%).

4-iso*Propylamino*-1 : 1-*diphenylpent*-2-*yn*-1-*ol*.—Similarly prepared from benzophenone (30 g.), 3-*iso*propylaminobut-1-yne (20 g.), and potassium hydroxide (30 g.), this *amino-alcohol* formed white prisms, m. p. 79—80°, from light petroleum (b. p. 60—80°) (Found : C, 82·0; H, 7·8; N, 4·95. $C_{20}H_{23}ON$ requires C, 81·9; H, 7·8; N, 4·8%). The *hydrochloride* formed white needles, m. p. 180°, from acetone (Found : N, 4·1. $C_{20}H_{23}ON,HCl$ requires N, 4·2%). The N-*acetyl* derivative, white needles from *cyclo*hexane, has m. p. 98—99° (Found : C, 78·65; H, 7·5; N, 4·65. $C_{22}H_{25}O_2N$ requires C, 78·8; H, 7·5; N, 4·2%).

4-*Diethylamino*-1-*phenyl*-1-p-*methoxyphenylpent*-2-*yn*-1-*ol*.—*p*-Methoxybenzophenone (18 g.), 3-diethylaminobut-1-yne (12 g.), and potassium hydroxide (15 g.), when similarly interacting in ether (75 c.c.), gave an oil (11 g.) which crystallised when set aside at 0° for 7 days. After recrystallisation from light petroleum (b. p. 40—60°) the *amino-alcohol* was obtained as white prisms, m. p. 50—52° (Found : C, 78·6; H, 8·3; N, 3·9. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·0; N, 4·2%). The *methiodide* formed white prisms, m. p. 152—153°, from acetone (Found : C, 57·1; H, 6·35; N, 2·5. $C_{23}H_{30}O_2NI$ requires C, 57·6; H, 6·3; N, 2·9%).

4-*Diethylamino*-1 : 1-*di*-p-*methoxyphenylpent*-2-*yn*-1-*ol*.—This was prepared in the usual way from *pp'*-dimethoxybenzophenone (5 g.), 3-diethylaminobut-1-yne (5 g.), and potassium hydroxide (5 g.). The *amino-alcohol* was obtained as white prisms, m. p. 100°, from light petroleum (b. p. 60—80°) (Found : C, 75·15; H, 7·7; N, 4·1. $C_{23}H_{29}O_3N$ requires C, 75·2; H, 7·9; N, 3·8%).

Diphenylethynylcarbinyl Acetate.—Diphenylethynylcarbinol (20 g.; Campbell, Cambell, and Eby, *J. Amer. Chem. Soc.*, 1938, **60**, 2882) was dissolved in dry pyridine (20 c.c.), and acetyl chloride (8 g.) added dropwise with stirring and cooling. After being kept at 40—50° for 3 hours, the mixture was poured into ice and water (200 g.), and the product extracted with ether and washed with dilute hydrochloric acid (twice) and water. The dried ($MgSO_4$) ethereal solution was distilled, giving 5 g. of an oil, b. p. 120°/1 mm., which solidified when kept for 14 days at 0° and recrystallised from *cyclo*hexane to give colourless prisms of *diphenylethynylcarbinyl acetate*, m. p. 79—80° (Found : C, 81·65; H, 5·5. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

4-*Morpholino*-1 : 1-*diphenylbut*-2-*yn*-1-*ol*.—(a) *From diphenylethynylcarbinyl acetate*. The acetate (30 g.), paraformaldehyde (5 g.), morpholine (12 g.), and dioxan (35 c.c.) were heated together at 100° for 16 hours. The dioxan was removed by distillation *in vacuo*, the residue dissolved in ether, and the ethereal solution washed with dilute sodium hydroxide solution and shaken with hydrochloric acid (125 c.c. of 2N.). The white solid (12 g.) which separated was collected and crystallised from water, giving 4-*morpholino*-1 : 1-*diphenylbut*-2-*yn*-1-*ol hydrochloride*, small prisms (from water), m. p. 203° (decomp.; bath preheated to 190°) (Found : C, 69·5; H, 6·0; N, 3·95. $C_{20}H_{21}O_2N,HCl$ requires C, 69·9; H, 6·4; N, 4·1%). The free *amine*, obtained by basification of a warm aqueous solution of the hydrochloride, formed colourless needles from methyl alcohol, m. p. 150—152° (Found : C, 78·4; H, 7·1; N, 4·8. $C_{20}H_{21}O_2N$ requires C, 78·2; H, 6·85; N, 4·6%). The *methiodide* formed plates, m. p. 168—170° (decomp.), from methyl alcohol (Found : C, 55·9; H, 5·45; N, 3·0. $C_{21}H_{24}O_2NI$ requires C, 56·1; H, 5·35; N, 3·1%). The acetyl derivative could not be prepared.

(b) *From diphenylethynylcarbinol*. The carbinol (21 g.), paraformaldehyde (4 g.), morpholine (10 g.), and dioxan (30 c.c.) were heated at 100° for 16 hours. The dioxan was removed by distillation *in vacuo*, the residue dissolved in ether and extracted with hydrochloric acid (20 c.c. of concentrated acid in 150 c.c. of water), and the aqueous acid layer basified with 10N-sodium hydroxide. The gummy precipitate was extracted with ether, and, after drying ($MgSO_4$) and evaporation, crystallised from methanol to give 4-morpholino-1 : 1-diphenylbut-2-yn-1-ol (0·3 g., 1%) as needles, m. p. 150—152°, identical with those obtained under (a), above.

4-*Dimethylamino*-1 : 1-*diphenylpent*-2-en-1-*ol*.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (5 g.), dissolved in methyl alcohol (100 c.c.), was hydrogenated at ordinary temperature and atmospheric pressure by using palladium on calcium carbonate as catalyst. After 40 minutes, absorption was complete (410 c.c.; calc. for H_2, 405 c.c.). After evaporation of the filtered solution *in vacuo*, the residue was recrystallised from light petroleum (b. p. 40—60°), giving 4-*dimethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol* (4 g.) as colourless plates, m. p. 72—74° (Found : C, 81·0; H, 7·95; N, 4·9. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2; N, 5·0%). The *methiodide* formed colourless prisms, m. p. 229—230° (decomp.; bath preheated to 210°), from water (Found : C, 56·55; H, 6·1; N, 3·25. $C_{20}H_{26}ONI$ requires C, 56·7; H, 6·1; N, 3·3%).

4-*Dimethylamino*-1 : 1-*diphenylpentan*-1-*ol*.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (5 g.), dissolved in methyl alcohol (100 c.c.), was hydrogenated at ordinary temperature and pressure by means of Raney nickel catalyst. The reduction proceeded in two stages, 415 c.c. (theory for H_2, 405 c.c.) being absorbed in one hour and 820 c.c. (theory for $2H_2$, 810 c.c.) in 12 hours, absorption then ceasing. Evaporation of the filtered solution *in vacuo* and crystallisation of the residue from light petroleum (b. p. 40—60°) gave 4-*dimethylamino*-1 : 1-*diphenylpentan*-1-*ol* (3·6 g.) as colourless prisms, m. p. 79—80° (Found : C, 80·7; H, 8·65; N, 5·4. $C_{19}H_{25}ON$ requires C, 80·5; H, 8·8; N, 4·95%). The *methiodide* formed colourless prisms, m. p. 237—238°, from methanol (Found : C, 56·4; H, 6·5; N, 3·05. $C_{20}H_{28}ONI$ requires C, 56·5; H, 6·6; N, 3·3%).

4-*Diethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol*.—This was obtained by reduction of 4-diethylamino-1 : 1-diphenylpent-2-yn-1-ol as described above for the dimethylamino-analogue. The *base* (61% yield) formed colourless plates, m. p. 68—70°, from light petroleum (b. p. 40—60°) (Found : C, 81·2; H, 8·5; N, 4·2. $C_{21}H_{27}ON$ requires C, 81·5; H, 8·7; N, 4·5%). The *methiodide* formed colourless plates, m. p. 190—192° (decomp.), from methyl alcohol (Found : C, 58·25; H, 6·35; N, 2·95. $C_{22}H_{30}ONI$ requires C, 58·5; H, 6·7; N, 3·1%).

4-*Diethylamino*-1 : 1-*diphenylpentan*-1-*ol*.—4-Diethylamino-1 : 1-diphenylpent-2-yn-1-ol (7 g.) in methyl alcohol (100 c.c.) was hydrogenated at room temperature and pressure in presence of Raney nickel catalyst. Absorption of 510 c.c. (theory for H_2, 513 c.c.) took 15 minutes, and that of 1400 c.c. 11 hours, after which the experiment was stopped although absorption was still occurring. The solvent was distilled from the filtered solution, and the presence of diethylamine in the distillate was established by isolation of its hydrochloride and picrolonate, and by the formation of *N*-α-naphthyl-*N'N'*-diethylurea, identical with authentic specimens. The residue after removal of methyl alcohol was dissolved in ether and extracted with dilute hydrochloric acid; the aqueous acid extract basified with 10N-sodium hydroxide, and the precipitated amine isolated with ether. Crystallisation of the residue from light petroleum (b. p. 40—60°) gave 4-*diethylamino*-1 : 1-*diphenylpentan*-1-*ol* (3·0 g.) as colourless plates, m. p. 92—94° (Found : C, 81·05; H, 8·9; N, 4·25. $C_{21}H_{29}ON$ requires C, 81·0; H, 9·3; N, 4·5%). The *methiodide* formed prisms, m. p. 178—180° (decomp.), from aqueous methyl alcohol (Found : C, 55·9; H, 7·1; N, 3·25. $C_{22}H_{32}ONI,H_2O$ requires C, 56·05; H, 7·2; N, 2·9%). Attempts to carry out the complete reduction with platinum or with palladium under pressure gave low yields of product and much fission to diethylamine.

4-*Morpholino*-1 : 1-*diphenylpent*-2-*en*-1-*ol*.—4-Morpholino-1 : 1-diphenylpent-2-yn-1-ol (5 g.) was reduced with a palladium–calcium carbonate catalyst as described for the dimethylamino-analogue. The *base* (4·4 g.) formed colourless elongated prisms, m. p. 93—94°, from light petroleum (b. p. 60—80°) (Found : C, 77·6; H, 7·6; N, 4·35. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%). The *methiodide* formed colourless prisms, m. p. 232° (decomp.; bath preheated to 210°), from methyl alcohol (Found : C, 56·35; H, 5·8; N, 2·7. $C_{22}H_{28}O_2NI$ requires C, 56·7; H, 6·0; N, 3·0%). Attempts to effect the saturation of the acetylenic linkage by means of platinum oxide gave a 16% yield of the ethylenic amine, and much morpholine. Raney nickel or palladium–calcium carbonate with hydrogen under pressure also gave a low yield of the ethylenic amine, and much fission occurred. Attempted further hydrogenation of the ethylenic amine gave the unchanged base in low yield and decomposition products, and reduction with sodium and liquid ammonia was also unsuccessful.

4-*Morpholino*-1 : 1-*diphenylbut*-2-*en*-1-*ol*.—4-Morpholino-1 : 1-diphenylbut-2-yn-1-ol (3·2 g.) was hydrogenated in dioxan (100 c.c.) at room temperature and atmospheric pressure with palladised calcium carbonate as catalyst. The hydrogenation was stopped after an absorption of 280 c.c. (absorption was still proceeding rapidly; theory for H_2, 240 c.c.), and after filtration and evaporation *in vacuo* gave a product (3 g.), m. p. 50—70°, which after three recrystallisations from methyl alcohol and two from light petroleum (b. p. 60—80°) gave 4-*morpholino*-1 : 1-*diphenylbut*-2-*en*-1-*ol* (2 g.) as needles, m. p. 88—89° (Found : C, 77·7; H, 7·4; N, 4·3. $C_{20}H_{23}O_2N$ requires C, 77·8; H, 7·4; N, 4·5%). The *methiodide* formed small prisms, m. p. 203° (decomp.; bath preheated to 190°), from water (Found : C, 55·7; H, 5·8; N, 3·1. $C_{21}H_{26}O_2NI$ requires C, 55·9; H, 5·8; N, 3·1%).

4-*Morpholino*-1 : 1-*diphenylbutan*-1-*ol*.—Hydrogenation was carried out as described for the semi-hydrogenation but the experiment was continued until absorption was complete. The *base* was obtained in 83% yield as silky needles, m. p. 128—130°, from light petroleum (b. p. 60—80°) (Found : C, 76·9; H, 8·0; N, 4·55. $C_{20}H_{25}O_2N$ requires C, 77·2; H, 8·0; N, 4·5%). The *methiodide* formed plates, m. p. 204° (decomp.; bath preheated to 190°), from water (Found : C, 55·5; H, 5·95; N, 3·4. $C_{21}H_{28}O_2NI$ requires C, 55·6; H, 6·2; N, 3·1%).

4-*Dimethylamino*-1 : 1-*diphenylpent*-1-*en*-3-*one*.—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (5 g.) was heated with dilute sulphuric acid (20 c.c. of concentrated acid in 100 c.c. of water) at 100° for 30 minutes. After cooling, 10N-sodium hydroxide (70 c.c.) was added, and the solution, after filtration from sodium sulphate, was extracted with ether to remove non-basic by-products. The aqueous layer was basified with 10N-sodium hydroxide and extracted with ether, and the ether dried ($MgSO_4$) and evaporated. The product crystallised from light petroleum (b. p. 40—60°) to give 4-*dimethylamino*-1 : 1-*diphenylpent*-1-*en*-3-*one* as yellowish needles, m. p. 52—54° (2·9 g., 58%) (Found : C, 81·3; H, 7·55; N, 5·1. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%). The *methiodide* formed cream-coloured plates, m. p. 220° (decomp.; bath preheated to 205°), from methanol (Found : C, 57·5; H, 5·7; N, 3·5. $C_{20}H_{24}ONI$ requires C, 57·0; H, 5·7; N, 3·3%).

This amino-ketone was very unstable; purified specimens decomposed to a brown liquid in 72 hours, and impure specimens were even less stable. For this reason the complete preparation and the utilisation of the product were always carried out in one day. One of the products of decomposition was non-basic, and it was possible to recover some of the amino-ketone from a partly decomposed sample by extraction with acid.

3-*Chloro*-4-*dimethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol.*—4-Dimethylamino-1 : 1-diphenylpent-2-yn-1-ol (1 g.) was heated at 100° for 5 minutes with water (10 c.c.) and 10N-hydrochloric acid (5 c.c.). After cooling to 45°, the insoluble hydrochloride was collected and crystallised from alcohol, giving 3-*chloro*-4-*dimethylamino*-1 : 1-*diphenylpent*-2-*en*-1-*ol hydrochloride* as white needles, m. p. 195° (decomp.) (0·5 g.) (Found : C, 63·25; H, 6·4. $C_{19}H_{22}ONCl,HCl,0\cdot5H_2O$ requires C, 63·15; H, 6·7%). The free *base* formed white prisms, m. p. 56—58°, from light petroleum (b. p. 40—60°) (Found : C, 72·7; H, 6·85; N, 4·4; Cl, 11·8. $C_{19}H_{22}ONCl$ requires C, 72·3; H, 7·0; N, 4·4; Cl, 11·3%). The *methiodide* formed white prisms, m. p. 227° (decomp.; bath preheated to 210°), from alcohol (Found : C, 52·55; H, 5·55; N, 2·95. $C_{20}H_{25}ONClI$ requires C, 52·5; H, 5·5; N, 3·0%).

The use of very dilute hydrochloric acid in this reaction gave only unchanged amino-alcohol after 24 hours' boiling; concentrated hydrochloric acid (15 minutes at 100°), however, caused disruption of the molecule and gave a non-basic tar from which benzophenone was isolated as its dinitrophenylhydrazone (m. p. and mixed m. p. 232°).

3-Chloro-4-dimethylamino-1 : 1-diphenylpent-2-en-1-ol regenerates the original acetylenic amine on treatment with 5% methanolic potassium hydroxide at 80° for 1½ hours. On catalytic reduction with Raney nickel and hydrogen at room temperature and pressure, 20% of the material is recovered unchanged, the rest being converted into a non-basic resin. When the alcohol is heated with 30% sulphuric acid, 4-dimethylamino-1 : 1-diphenylpent-1-en-3-one is formed.

4-*Diethylamino*-1 : 1-*diphenylpent*-1-*en*-3-*one.*—4-Diethylamino-1 : 1-diphenylpent-2-yn-1-ol hydrochloride (3·3 g.), dissolved in water (50 c.c.), was boiled under reflux for 24 hours. After cooling, some oil was removed by ether-extraction, the aqueous layer was basified with dilute sodium hydroxide solution, and the product (a sticky solid) extracted with ether. After drying ($MgSO_4$) and evaporation, a viscous yellow oil was obtained, which on crystallisation from light petroleum gave only a low yield of recovered diethylaminodiphenylpentynol, m. p. 81—83°. Methylation of the crude oil with methyl iodide in acetone, however, gave pale yellow needles, m. p. 193°, from alcohol. This was not identical with the methiodide of the original amine, and is probably 4-*diethylamino*-1 : 1-*diphenylpent*-1-*en*-3-*one methiodide* (Found : C, 58·5; H, 6·4; N, 3·6; I, 27·6. $C_{22}H_{28}ONI$ requires C, 58·8; H, 6·3; N, 3·1; I, 28·3%).

3-*Chloro*-4-*morpholino*-1 : 1-*diphenylpent*-2-*en*-1-*ol.*—4-Morpholino-1 : 1-diphenylpent-2-yn-1-ol (10 g.) was heated with hydrochloric acid (36%; 50 c.c.) and water (100 c.c.) at 80—90° for 5 minutes. After cooling to 40°, the precipitated hydrochloride (5 g., 41%) was collected and recrystallised from alcohol, giving 3-*chloro*-4-*morpholino*-1 : 1-*diphenylpent*-2-*en*-1-*ol hydrochloride* as needles, m. p. 176° (decomp.) (Found : C, 63·55; H, 6·3; N, 3·3. $C_{21}H_{24}O_2NCl,HCl$ requires C, 63·9; H, 6·3; N, 3·6%). The free *base*, regenerated from the hydrochloride with sodium hydroxide, separated from methyl alcohol in small plates, m. p. 105—106° (Found : C, 70·4; H, 6·9; N, 4·0; Cl, 10·7. $C_{21}H_{24}O_2NCl$ requires C, 70·6; H, 6·7; N, 3·9; Cl, 10·1%). The *methiodide* formed minute needles, m. p. 198° (decomp.), from methyl alcohol (Found : C, 52·5; H, 5·4; N, 2·5. $C_{21}H_{27}O_2NClI$ requires C, 52·8; H, 5·4; N, 2·8%).

Treatment of the base with methanolic potassium hydroxide regenerated 4-morpholino-1 : 1-diphenylpent-2-yn-1-ol, m. p. and mixed m. p. 140—142°. Reduction with Raney nickel and hydrogen at room temperature and pressure gave 20% of recovered chloro-amine and much unidentified tar.

4-*Morpholino*-1 : 1-*diphenylpent*-1-*en*-3-*one.*—4-Morpholino-1 : 1-diphenylpent-2-yn-1-ol (2 g.) was dissolved in dilute sulphuric acid (8 c.c. of concentrated acid and 40 c.c. of water), and the solution heated on the steam-bath for 30 minutes. The cooled solution was made strongly alkaline with 10N-sodium hydroxide, and the precipitated oil extracted with ether. The ethereal solution was extracted with 2N-hydrochloric acid, and the acidic extract basified (10N-NaOH), and again extracted with ether. Evaporation of the ether gave a yellow oil which could not be induced to crystallise. Addition of dry hydrogen chloride in ether afforded the *hydrochloride*, m. p. 184—185°, as white needles from alcohol (Found : C, 70·3; H, 6·75; N, 3·9. $C_{21}H_{23}O_2N,HCl$ requires C, 70·5; H, 6·7; N, 3·9%), which depressed the m. p. (186°) of the hydrochloride of the starting material. Treatment of the crude oil with methyl iodide gave the *methiodide* as yellow prisms, m. p. 197° (decomp.), from alcohol (Found : C, 57·2; H, 6·0; N, 2·9. $C_{22}H_{26}O_2NI$ requires C, 57·0; H, 5·7; N, 3·0%). The methiodide depressed the m. p. (202—203°) of the (white) methiodide of the starting material. The same material, identified as the hydrochloride and methiodide, was formed when 3-chloro-4-morpholino-1 : 1-diphenylpent-2-en-1-ol (above) was treated at 100° for 3 hours with 35% sulphuric acid.

IMPERIAL CHEMICAL INDUSTRIES LTD. (DYESTUFFS DIVISION),
BLACKLEY, MANCHESTER, 9.

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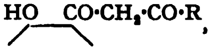
75. *The Effect of Bond Structure on the Transformation of* o-*Aroyloxyacetoarones into* o-*Hydroxydiaroylmethanes. Baker–Venkataraman Transformation.*

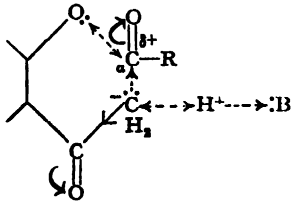
By N. V. Nowlan, P. A. Slavin, and T. S. Wheeler.

The experimental results indicate that the Baker–Venkataraman transformation of *o*-aroyloxyacetoarones into *o*-hydroxydiaroylmethanes takes place more rapidly across the 2 : 3-bond (single bond) in naphthalene than across the 1 : 2-bond (double bond). This is attributed to ester-type neutralisation across the double bond, and is in accordance with the view (Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291) that the transformation involves a base-catalysed intramolecular Claisen condensation. Preliminary results with *o*-aroyloxyacetylindanes do not seem to be in accord with the Mills–Nixon view of bond distribution in indane.

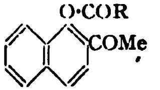
The tendency of *o*-hydroxydiaroylmethanes,  $\overset{HO}{} \; \overset{CO\cdot CH_2\cdot CO\cdot R}{}$, to undergo spontaneous cyclisation to the corresponding flavones when R contains an electrophilic (nitro-) group is discussed. A number of new 4-pyrones are described.

It has not been found possible to transform *o*-arylsulphonyloxyacetophenones.

The transformation of *o*-aroyloxyacetoarones into *o*-hydroxydiaroylmethanes (Baker, *J.*, 1933, 1381; Mahal and Venkataraman, *J.*, 1934, 1767) has been shown by Doyle *et al.* (*Proc. Roy. Dublin Soc.*, 1948, **24**, 291) to be a base-catalysed intramolecular Claisen condensation involving a nucleophilic displacement of oxygen on carbon as indicated by the transition compound (I). This paper describes an investigation of this transformation across the $C_{(1)}$–$C_{(2)}$ and $C_{(2)}$–$C_{(3)}$ bonds of naphthalene, which have as regards the chemical reactivity of naphthalene compounds the quality, respectively, of double and single bonds [cf. Fieser, "Organic Chemistry" (Gilman), 1943, Vol. I, 145]. The experimental work was concerned mainly with the base-catalysed transformation of *o*-(nitrobenzoyloxy)acetonaphthones (II, III, and IV; R = *o*-, *m*-, or *p*-nitro- or 3 : 5-dinitro-phenyl) into the corresponding *o*-hydroxy-diketones, $C_{10}H_6(OH)\cdot CO\cdot CH_2\cdot CO\cdot R$, which in some instances cyclised spontaneously to form the benzflavone (V). The transformation of other 2-acyloxy-3-acetonaphthones (IV; R = Me, Ph, styryl, or 2-methoxy-3-naphthyl), and of some esters of *o*-hydroxyacetylindanes (VI; R = Me, Ph, and *p*-nitrophenyl) and (VII), was also investigated. Attempts to transform benzene- and toluene-sulphonic esters of the *o*-hydroxyacetonaphthones (see Table III) using a variety of basic catalysts (see Doyle *et al.*, *loc. cit.*) were unsuccessful: the sulphonyl group, though electrophilic, is less so than the carbonyl group (Kohler and Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 1316; Connor *et al.*, *ibid.*, 1936, **58**, 1386). When 2-benzenesulphonyloxy-3-acetonaphthone was treated with triphenylmethylsodium, a compound giving analytical figures corresponding to $C_{56}H_{44}O_2S$ [? 2 : 3-$C_{10}H_6$(COMe)·O·SPh$(CPh_3)_2$] was obtained. Transformation of the sulphonic esters was also attempted using boron trifluoride as an acid catalyst (see Breslow and Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2385) but without success.



(I.) (:B = base.)



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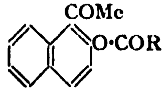

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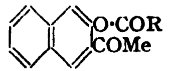

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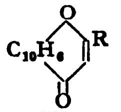

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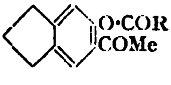
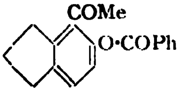


(VI.)



(VII.)

Results with o-Acyloxyacetonaphthones.—The trend of the results obtained with the nitro-esters summarised in Table I, while not conclusive, indicates that generally transformation takes place across the $C_{(2)}$–$C_{(3)}$ single-type bond more rapidly than across the $C_{(1)}$–$C_{(2)}$ double-type bond. Comparative experiments with 2-benzoyloxy-1-acetonaphthone (III; R = Ph) (Bhalla *et al.*, *J.*, 1935, 870) and *2-benzoyloxy-3-acetonaphthone* (IV; R = Ph) gave, similarly, more rapid transformation with the latter compound. Smooth and rapid transformation was also obtained with *2-cinnamoyloxy-3-acetonaphthone* (IV; R = styryl) and 2-(*2-methoxy-3-naphthoyloxy*)-*3-acetonaphthone* (IV; R = 2-methoxy-3-naphthyl). It was not found possible to transform 2-acetoxy-3-acetonaphthone (IV; R = Me) (Fries and Schimmelschmidt, *Ber.*,

TABLE I.

Results with nitrobenzoyloxyacetonaphthones.

(II, III, and IV; R = *o*-, *m*-, or *p*-nitro- or 3 : 5-dinitro-phenyl.)

	Acetonaphthone.					
	1-Hydroxy-2-acetonaphthone (II).		2-Hydroxy-1-acetonaphthone (III).		2-Hydroxy-3-acetonaphthone (IV).	
Aroyl radical.	Reaction time, mins.	Yield,[1] %.	Reaction time, mins.	Yield,[1] %.	Reaction time, mins.	Yield,[1] %.
2-Nitrobenzoyl-	2	26 D	6	2 DF	2	30 DF
3-Nitrobenzoyl-	7	22 D	8	21 F	1	30 D
4-Nitrobenzoyl-	5	58 D	7	28 D	<1	46 D
3 : 5-Dinitrobenzoyl-	5	Tar	6	50 F[2]	1	3 F

These transformations were carried out under controlled conditions in boiling pyridine with potassium hydroxide as base. For details see the Experimental section. Potassium hydroxide was chosen after a number of the bases used by Doyle *et al.* (*loc. cit.*) had been tested.

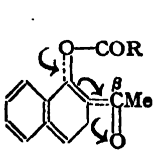
[1] Yields are calculated on the aroyloxyacetonaphthone. D indicates yield of diketone; F shows yield of flavone when produced by spontaneous cyclization of diketone; DF gives yield of flavone obtained by cyclization of material (crude diketone) which could not readily be purified.

[2] 3′ : 5′-*Dinitro*-3-(3 : 5-*dinitrobenzoyl*)-5 : 6-*benzflavone* was the probable product of the transformation.

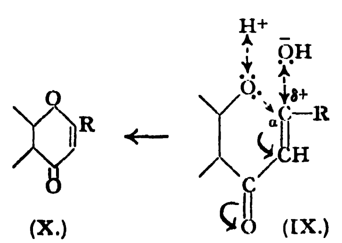
1925, 58, 2835). *o*-Acetoxyacetoarones (I; R = Me) are difficult to transform (cf. Baker, *loc. cit.*; Virkar and Wheeler *J.*, 1939, 1679; Geissman, *J. Amer. Chem. Soc.*, 1949, 71, 1498) as the anionoid effect of the methyl group reduces the electrophilic nature of $C_{(\alpha)}$ (I). Gowan (private communication) has, however, succeeded in transforming *o*-acetoxyacetophenone into *o*-hydroxybenzoylacetone using triphenylmethylsodium as the basic catalyst.

These results support the view of Doyle *et al.* (*loc. cit.*) as to the mechanism of the transformation. The mobile π electrons of the $C_{(1)}$–$C_{(2)}$ bond facilitate ester-type neutralisation of the carbonyl carbon $C_{(\beta)}$ (VIII); such neutralisation occurs less readily across the $C_{(2)}$–$C_{(3)}$ bond in which the density of electrons is low (see Pullman, *Ann. Chim.*, 1947, 2, 5). The occurrence of such neutralisation across the $C_{(1)}$–$C_{(2)}$ bond is shown by the exceptionally high basic strength of 2-nitro-3-naphthylamine as compared with 2-nitro-1-naphthylamine and 1-nitro-2-naphthylamine (cf. Bryson, *Trans. Faraday Soc.*, 1949, 45, 257; Hodgson and Turner, *J.*, 1943, 635). The argument is supported by the non-existence of 2 : 3-naphthaquinone; an *o*-quinonoid form is involved in the type of neutralisation shown in (VIII) (see Waters, *J.*, 1948, 727).

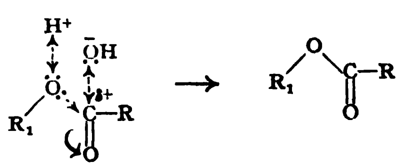
Preliminary Results with o-*Aroyloxyacetylindanes.*—5-*Benzoyloxy*-6-*acetylindane* (VI; R = Ph) was found in comparative experiments to be transformed into the corresponding *diketone* more rapidly than was 5-*benzoyloxy*-4-*acetylindane* (VII). This result is unexpected if the Mills–Nixon structure (*J.*, 1930, 2510), which is shown in (VI) and (VII), is assumed for indane.



(VIII.)



(X.) (IX.)



(IX*a*.) (X*a*.)

However, though Baker's well-known investigation on chelation effects (*J.*, 1937, 476) supports this structure for *o*-hydroxyacetylindanes, the results of extensive work on the reactivity of indane and of its derivatives indicate that, if bond fixation is present, it is not so well-defined as in the naphthalene series, but is more sensitive to the substituents present and to the reagents employed [see Fieser, *op. cit.*, p. 139; Hippchen, "On the arrangement of the double bonds in hydrindene (indane)," F.I.A.T. Final Report, No. 1033 (1947); "Elsevier's Encyclopædia of Organic Chemistry," 1948, 12, *A*, 103; Springall *et al.*, *J.*, 1949, 1524]. It is hoped to investigate further the transformation of esters of the type shown in (VI) and (VII). 5-Acetoxy-6-acetylindane (VI; R = Me) (Baker, *loc. cit.*) could not be transformed.

Flavone Formation.—It will be seen from Table I that three of the nitro-diketones (indicated by F) cyclised, when formed, to the flavone (cf. Doyle *et al., loc. cit.*). This cyclisation is of course analogous to esterification (IX; IX*a*; X; X*a*); it involves a nucleophilic displacement of hydroxyl on carbon (see Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686) and is therefore promoted by the presence, in R, of an electrophilic (nitro-) group, which increases the cationoid activity of $C_{(\alpha)}$ (IX). It will be noted that 2-(3 : *5-dinitrobenzoyloxy*)-1-*acetonaphthone* (III; R = 3 : 5-dinitrophenyl) yielded directly a compound giving analytical figures corresponding to the related 3-aroylated *flavone* (Table I, footnote 2).

EXPERIMENTAL.

Preparation of o-*Hydroxyacetoarones and their Esters.*—1-Hydroxy-2-acetonaphthone (Witt and Braun, *Ber.*, 1914, **47**, 3216), 2-hydroxy-1-acetonaphthone (Fries, *Ber.*, 1921, **54**, 709), 2-hydroxy-3-acetonaphthone (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2835), 5-hydroxy-6-acetylindane, and 5-hydroxy-4-acetylindane (Baker, *J.*, 1937, 476) were synthesised as described by the authors cited. In this preparation of 1-hydroxy-2-acetonaphthone it was found essential to keep the temperature of the reaction mixture below 140°, otherwise 1-hydroxy-2 : 4-diacetylnaphthalene was produced.

The esters were prepared by the pyridine–acid chloride method (cf. Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291); the yields were usually over 60%. Completion of esterification was determined by extracting an acidified sample of the reaction mixture with chloroform, diluting the extract with alcohol, and testing for free *o*-hydroxy-diketone with alcoholic ferric chloride. Serial numbers have been assigned to the carboxylic esters to facilitate cross-reference.

Those of the sulphonic esters which did not solidify rapidly when the reaction mixture was acidified were extracted with chloroform, and the extracts were washed with aqueous sodium carbonate and with water and dried (Na_2SO_4). The residue obtained on removal of the solvent was distilled at about 10^{-3} mm. before recrystallisation.

Mononitrobenzoyloxyacetonaphthones.—These compounds (see Tables I and II) were colourless to yellow, excepting No. 4 which was red.

TABLE II.

y-(x-*Nitrobenzoyloxy*)-z-*acetonaphthones.*

(II, III, and IV; R = *o*-, *m*-, and *p*-nitrophenyl) ($C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9; N, 4·2%).

	Ester.					Found, %.		
Serial no.	*x*.	*y*.	*z*.	M. p.	Crystallizing solvent.	C.	H.	N.
1	2′	1	2	115—116°	Alcohol–dioxan	68·0	4·1	4·3[1]
2	3′	1	2	151—152	Alcohol	—	—	4·4[2]
3	4′	1	2	150—151	Alcohol–dioxan	68·3	3·9	4·3[2]
4	2′	2	1	146—148	Acetone–aqueous alcohol	67·3	3·9	4·3[1]
5	3′	2	1	174—176	Chloroform	68·1	3·9	4·5[1]
6	4′	2	1	137—138	Acetone–aqueous alcohol	67·3	3·9	4·2[1]
7	2′	2	3	165	Alcohol–dioxan	68·2	4·1	4·2[1]
8	3′	2	3	146—148	Alcohol–dioxan	67·8	3·9	4·0[1]
9	4′	2	3	177—179	Alcohol–dioxan	67·7	3·9	4·0[1]

[1] New compound. [2] Virkar, *J. Univ. Bombay*, 1942, **11**, 136.

Dinitrobenzoyloxyacetonaphthones (see Table I).—The molecular formula, $C_{19}H_{12}O_7N_2$, for these compounds requires C, 60·0; H, 3·1; N, 7·4%. 1-(3 : 5-*Dinitrobenzoyloxy*)-2-*acetonaphthone* (II; R = 3 : 5-dinitrophenyl) (10) (from chloroform), m. p. 209—212° (decomp.) (Found: C, 59·7; H, 3·3; N, 7·4%), 2-(3 : *5-dinitrobenzoyloxy*)-1-*acetonaphthone* (III; R = 3 : 5-dinitrophenyl) (11) [from chloroform–light petroleum (b. p. 60—80°)], m. p. 200—202° (Found: C, 60·2; H, 3·2; N, 7·8%), and 2-(3 : *5-dinitrobenzoyloxy*)-3-*acetonaphthone* (IV; R = 3 : 5-dinitrophenyl) (12) [from chloroform–light petroleum (b. p. 40—60°)], m. p. 173° (Found: C, 59·9; H, 3·2; N, 7·3%), were readily obtained (*ca.* 80% yield) as pale yellow crystals by the pyridine–acid chloride method.

Other Carboxylic Acid Esters.—*2-Benzoyloxy-3-acetonaphthone* (IV; R = Ph) (13) (from ligroin), m. p. 111° (Found: C, 78·5; H, 4·7. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%), *2-cinnamoyloxy-3-acetonaphthone* (IV; R = styryl) (14) (from ligroin), m. p. 121° (Found: C, 79·6; H, 5·2. $C_{21}H_{16}O_3$ requires C, 79·7; H, 5·1%), 2-(*2-methoxy-3-naphthoyloxy*)-*3-acetonaphthone* (IV; R = 2-methoxy-3-naphthyl) (15) (from benzene and alcohol), m. p. 191° (Found: C, 77·7; H, 5·0. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%), *5-benzoyloxy-6-acetylindane* (VI; R = Ph) (16) (from aqueous alcohol), m. p. 87—88° (Found: C, 77·0; H, 5·9. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%), 5-(p-*nitrobenzoyloxy*)-6-*acetylindane* (VI; R = *p*-nitrophenyl) (17) (from aqueous alcohol), m. p. 104—105° (Found: C, 66·6; H, 4·8; N, 4·3. $C_{18}H_{15}O_5N$ requires C, 66·5; H, 4·6; N, 4·3%), and *5-benzoyloxy-4-acetylindane* (VII) (18) (from aqueous methyl alcohol and ligroin), m. p. 89—90° (Found: C, 77·1; H, 5·6. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%), were obtained as colourless crystals.

Sulphonic Acid Esters.—Results for these compounds, all colourless, are given in Table III.

Action of Triphenylmethylsodium on 2-Benzenesulphonyloxy-3-acetonaphthone.—2-Benzenesulphonyloxy-3-acetonaphthone (0·5 g.) contained in a reaction flask filled with nitrogen was treated with an ethereal solution of triphenylmethylsodium, prepared, stored, and delivered into the reaction flask in an atmosphere of nitrogen using the procedure of Hauser and Hudson ("Organic Reactions," 1942, Vol. I, 286). Addition of the reagent was discontinued when the red colour of its solution was no longer discharged. The mixture was shaken for 1 hour and treated with water. The insoluble *product* (0·5 g.)

separated from chloroform and from glacial acetic acid in colourless crystals, m. p. 184°, insoluble in aqeuous alkai, acetone, and ether, soluble in chloroform, and unaffected by hot hydrobromic acid in glacial acetic acid (Found : C, 86·5, 86·4, 86·3, 86·5; H, 5·8, 5·9, 5·5, 5·6; S, 4·4, 4·7. $C_{66}H_{44}O_2S$ requires C, 86·2; H, 5·6; S, 4·1%).

TABLE III.

Sulphonic acid esters, x-R-*sulphonyloxy*-y-*acetonaphthones.*[1]

(*A*; R = benzene : $C_{18}H_{14}O_4S$ requires C, 66·3; H, 4·3; S, 9·8%.
B; R = toluene : $C_{19}H_{16}O_4S$ requires C, 67·1; H, 4·7; S, 9·4%.)

	Ester.				Found, %.		
R.	*x*.	*y*.	M. p.	Crystallizing solvent.	C.	H.	S.
A; Benzene	2	1	72—74°	Aqueous alcohol	66·2	4·4	9·6
,,	2	3	84—86	Alcohol	66·1	4·3	9·4
B; *o*-Toluene	1	2	63—65	Alcohol	66·9	4·9	9·5
,,	2	1	60—62	Light petroleum (b. p. 60—80°)	67·0	4·8	9·4
,,	2	3	110—112	Alcohol	67·0	4·8	9·0
p-Toluene	1	2	99—101	Aqueous alcohol	66·9	4·7	9·6
,,	2	1	98—99	Alcohol	67·3	4·9	9·3
,,	2	3	84—86	Alcohol	66·8	4·7	9·0

[1] These compounds are new.

Preparation of 1 : 3-*Diketones.—Transformation into ketones of the nitro-esters listed in Table II.* Potassium hydroxide (*ca.* 0·1 g.) was crushed between warm dry filter-papers and rapidly transferred to a boiling pyridine solution (5 ml.) of the ester (0·5 g.) to be transformed. Heating under reflux was continued until the solution, at first red, became brown, and solid separated. The mixture was cooled, diluted with water (20 ml.), and filtered. The filtrate was brought to pH 6 (glass electrode) with glacial acetic acid (*ca.* 0·4 ml.), and after an hour the precipitated diketone was collected and crystallised or, if difficult to purify, cyclised to the flavone. The presence of a nitro-group, particularly in the *ortho*-position, promotes the formation of resin and, if heating was continued until the solution became black, an unworkable product was obtained. Acidification beyond pH 6 caused precipitation of resin. Results for the nitrobenzoyl-*o*-hydroxynaphthoylmethanes prepared in this way are given in Table IV. The colour of these compounds varied from yellow to orange.

TABLE IV.

x-*Nitrobenzoyl*-y-*hydroxy*-z-*naphthoylmethanes.*

($C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9; N, 4·2%.)

	Diketone.					Found, %.		
Corresponding ester no. of Table II.	*x*.	*y*.	*z*.	M. p.	Crystallizing solvent.	C.	H.	N.
1	2	1′	2′	173—175°	Aqueous acetone	67·8	4·1	4·1 [1]
2	3	1′	2′	191	Acetone	68·4	3·9	4·3 [2]
3	4	1′	2′	222—224	Tetrahydrofurfuryl alcohol	67·5	4·0	4·2 [2]
6	4	2′	1′	168—170	Alcohol	67·9	4·0	4·2 [1]
8	3	2′	3′	182—183	Acetone	67·7	3·9	4·5 [1]
9	4	2′	3′	228—230	Acetone	68·1	4·2	4·2 [1]

[1] New compound. [2] Virkar, *loc. cit.*

Transformation of other esters of o-*hydroxyacetonaphthones. Benzoyl*-2-*hydroxy*-3-*naphthoylmethane.* A solution of 2-benzoyloxy-3-acetonaphthone (IV; R = Ph) (ester no. 13) (1·2 g.) in pyridine (5 ml.) was treated with alcoholic sodium ethoxide (3 ml. of a solution containing 1 g. of sodium in 25 ml. of alcohol). The sodium salt of the diketone separated rapidly. The mixture was diluted with water and acidified with 10% hydrochloric acid. The solid (1·0 g.) thus obtained crystallised from aqueous alcohol in yellow needles, m. p. 129—130° (Found : C, 78·4; H, 4·8. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%). In comparative experiments (ester, 45 mg.; pyridine, 1 ml.; sodium ethoxide, 0·5 ml. of the solution referred to above) 2-benzoyloxy-1-acetonaphthone (Ullal, Shah, and Wheeler, *J.*, 1940, 1499) showed a slower rate of transformation. No effect was apparent until 30 minutes after addition of the base, as compared with the immediate precipitate obtained with the 2 : 3-compound.

Cinnamoyl-2-*hydroxy*-3-*naphthoylmethane* (from glacial acetic acid), m. p. 160° (Found : C, 79·3; H, 4·9. $C_{21}H_{16}O_3$ requires C, 79·7; H, 5·1%), and 2-*hydroxy*-2′-*methoxy*-3 : 3′-*dinaphthoylmethane* (from glacial acetic acid), m. p. 181—182° (Found : C, 77·1; H, 5·0. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%), were prepared as yellow crystals from the corresponding esters (nos. 14 and 15 respectively). As with 2-benzoyloxy-3-acetonaphthone (see above) the transformations were immediate.

Transformation of esters of o-*hydroxyacetylindanes.* 5-*Hydroxy*-6-*benzoylacetylindane.* A solution of 5-benzoyloxy-6-acetylindane (VI; R = Ph) (ester No. 16) (0·5 g.) in pyridine (5 ml.) was treated with solid potassium hydroxide (0·15 g.) previously crushed in a hot mortar, and the mixture was kept overnight. The yellow solid (0·47 g.) obtained when the reaction product was mixed with excess of 10% hydrochloric acid separated from aqueous alcohol in yellow needles, m. p. 99—101° (Found : C, 77·1; H, 5·8. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%). 5-*Hydroxy*-6-p-*nitrobenzoylacetylindane* (from aqueous dioxan), m. p. 225—227° (Found: C, 66·1; H, 4·5; N, 4·3. $C_{18}H_{15}O_5N$ requires C, 66·5; H, 4·6; N, 4·3%), and *5-hydroxy-4-benzoylacetylindane* (from aqueous alcohol), m. p. 114—115° (Found: C, 77·2; H, 5·8. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%), were similarly prepared as yellow crystalline solids from the corresponding esters (nos. 17 and 18). The yields were respectively 75 and 85%.

Comparative experiments were made on the rates of transformation of 5-benzoyloxy-6-acetylindane (VI; R = Ph) and 5-benzoyloxy-4-acetylindane (VII) using solid potassium hydroxide in pyridine as described above. With 5-benzoyloxy-6-acetylindane there was an immediate colour change and separation of the salt of the diketone was complete in 30 minutes. With the 5 : 4-isomer, 30 minutes elapsed before separation of the diketone salt commenced, and complete reaction required some hours.

Preparation of 4-Pyrones.—These compounds (flavones; benzchromones; indanopyrones) were obtained from esters, through diketones, by the following three methods:

A. The diketone was boiled with glacial acetic acid containing a few drops of concentrated hydrochloric acid, and the pyrone formed was separated by addition of hot water until a permanent opalescence was produced. The liquid was then slowly cooled (see Doyle *et al.*, *loc. cit.*). The yields were usually quantitative.

B. The crude product (diketone) of the transformation which could not readily be purified was cyclised by Method A.

C. The flavone resulted directly by spontaneous cyclisation of the diketone formed in the transformation reaction.

Mononitrobenzoflavones. Table V summarises results for the mononitrobenzoflavones obtained from the esters listed in Table II.

TABLE V.

x-*Nitro*-y : z-*benzflavones.*

($C_{19}H_{11}O_4N$ requires C, 71·9; H, 3·5; N, 4·4%.)

Corresponding ester no. in Table II.	Nitrobenzflavone. *x.*	*y.*	*z.*	M. p.	Found, %. C.	H.	N.	Method of preparation of flavone.
1	2′	7	8	222—224°	71·7	3·9	4·1	A[1]
2	3′	7	8	258	71·7	3·5	—	A[2]
3	4′	7	8	296	72·2	3·7	4·2	A[2]
4	2′	5	6	214—215	71·5	3·8	4·4	B[1]
5	3′	5	6	256—257	72·3	3·9	4·4	C[1]
6	4′	5	6	282—284	71·4	3·6	4·3	A[1]
7	2′	6	7	192—194	71·7	3·2	4·6	B[1]
8	3′	6	7	248—250	72·0	3·7	4·8	A[1]
9	4′	6	7	264	71·7	3·7	4·5	A[1]

These compounds, No. 1 excepted, were crystallised from glacial acetic acid; for No. 1 acetone–alcohol was used. They separated from the solvent in colourless to pale yellow crystals.

[1] New compound. [2] Virkar, *loc. cit.*

Dinitrobenzflavones. 3′ : 5′-*Dinitro*-3-(3 : 5-*dinitrobenzoyl*)-5 : 6-*benzflavone* (from glacial acetic acid and tetrahydrofurfuryl alcohol), m. p. 267—269° (Found: C, 56·8; H, 2·5; N, 10·0. $C_{26}H_{12}O_{11}N_4$ requires C, 56·1; H, 2·2; N, 10·1%), was obtained directly (method C) as a red powder in the transformation of 2-(3 : 5-dinitrobenzoyloxy)-1-acetonaphthone (III; R = 3 : 5-dinitrophenyl) (ester no. 11). 3′ : 5′-*Dinitro*-6 : 7-*benzflavone* (from dioxan), m. p. 330° (decomp.) (Found: C, 62·5; H, 2·9; N, 7·6. $C_{19}H_{10}O_6N_2$ requires C, 63·0; H, 2·8; N, 7·7%), was similarly obtained as a yellow powder from 2-(3 : 5-dinitrobenzoyloxy)-3-acetonaphthone (IV; R = 3 : 5-dinitrophenyl) (ester no. 12).

Other pyrones. The following 4-pyrones were prepared from the corresponding diketones using method A. The number of the ester corresponding to the diketone is given in brackets. 6 : 7-Benzflavone (linear naphthaflavone) (13) (colourless; from benzene–ligroin), m. p. 173° (Virkar and Wheeler, *J.*, 1939, 1682, give 171—172°) (Found: C, 83·3; H, 4·5. Calc. for $C_{19}H_{12}O_2$: C, 83·8; H, 4·4%); 2-*styryl*-6 : 7-*benzchromone* (14) (pale yellow; from benzene–ligroin), m. p. 168° (Found: C, 84·2; H, 4·9. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%); 2-(2-*methoxy*-3-*naphthyl*)-6 : 7-*benzchromone* (15) (pale yellow; from benzene–ligroin), m. p. 214° (Found: C, 81·3; H, 3·5. $C_{24}H_{16}O_3$ requires C, 81·8; H, 4·5%); 6-*phenylindano*(5′ : 6′-2 : 3)-4-*pyrone* (16) (colourless; from aqueous acetic acid), m. p. 161—162° (Found: C, 82·3; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%); 6-(p-*nitrophenyl*)*indano*(5′ : 6′-2 : 3)-4-*pyrone* (17) (yellow; from aqueous acetic acid), m. p. 265—267° (Found: C, 70·3; H, 4·3; N, 4·7. $C_{18}H_{13}O_4N$ requires C, 70·4; H, 4·2; N, 4·6%).

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UNIVERSITY COLLEGE, DUBLIN.

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76. *Some Physico-chemical Properties of Acridine Antimalarials, with Reference to their Biological Action. Part I. Basic Dissociation Constants and Reduction Potentials.*

By D. Ll. Hammick and S. F. Mason.

Two homologous series of acridine antimalarials analogous to Mepacrine (I) have been examined with the polarograph over a range of concentrations and pH values in order to measure reduction potentials and other quantities defining the oxidation–reduction behaviour of these compounds. Further measurements have been made of the pH values of aqueous and aqueous-alcoholic solutions of the dihydrochlorides of these derivatives in the presence of various amounts of alkali, and from the results obtained the basic dissociation constants of the compounds have been calculated. No definite correlation between antimalarial activity and either basicity or reduction potential has been observed.

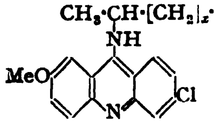
Chemotherapeutic agents belonging to the same structural type appear to act on a given organism by the same or very similar mechanisms. The efficacy of their action varies widely however, and in some cases seems to depend on the values of certain physico-chemical properties, as Bell and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 2905) have discovered for the sulphonamides, and Albert and his co-workers (*Brit. J. Exp. Path.*, 1945, **26**, 160) for the simple aminoacridines.

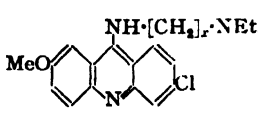
In the present work an attempt has been made to correlate the values of some physico-chemical properties of acridine antimalarials with their relative biological activities. The properties thought possibly relevant were selected by considering the nature of the action of Mepacrine on enzyme systems, bacteria, and the malaria parasite. Amongst other things, Mepacrine (I) interferes with the growth of bacteria by competing with natural bases, notably polyamines (Silverman and Evans, *J. Biol. Chem.*, 1944, **154**, 521), and also with the hydrogen carrier, riboflavin (Madinaveitia, *Biochem. J.*, 1946, **40**, 373; Haas, *J. Biol. Chem.*, 1944, **155**, 321). The competition of two bases and two oxidation–reduction systems for a common substrate may be said to be governed physico-chemically by the relative basicities and reduction potentials of the two substances. Thus it was thought that the relative values of the dissociation constants and the half-wave potentials of a structurally similar series of acridine antimalarials might possibly be related to their relative antimalarial activities.

Experimental.

Preparation of Materials.—Two homologous series of acridine antimalarials were prepared by standard methods (Magidson *et al.*, *Ber.*, 1936, **69**, 396; Breslow, *J. Amer. Chem. Soc.*, 1941, **63**, 156; 1946, **68**, 100). One, homologous with Mepacrine (I; $x = 3$), consisted of four members (I) having $x = 1$ to 4; the other possessed straight side-chains, six compounds (II) being prepared having $x = 2$ to 7.

(I.)





(II.)

2-*Chloro*-5-(1-*diethylamino*-2-*propylamino*)- (cf. I; $x = 1$), m. p. 223° (Found: C, 56·6; H, 6·4; N, 9·3; Cl, 22·4. $C_{21}H_{26}ON_3Cl,2HCl,H_2O$ requires C, 56·45; H, 6·7; N, 9·4; Cl, 23·05%), and 2-*chloro*-5-(7-*diethylaminoheptylamino*)-7-*methoxyacridine dihydrochloride* (cf. II; $x = 7$), m. p. 240—242° (Found: C, 58·4; H, 7·2; N, 8·3; Cl, 21·0. $C_{25}H_{34}ON_3Cl,2HCl$ requires C, 58·3; H, 7·5; N, 8·8; Cl, 22·1%), 5-(3-diethylaminopropylamino)acridine dihydrochloride, m. p. 230—232° (cf. Gupta, *J. Indian Chem. Soc.*, 1945, **22**, 364, who give m. p. 230°), and the compounds listed in Table I were examined.

Table I.

2-*Chloro*-5-(*R*)-7-*methoxyacridine dihydrochlorides* (cf. I and II).

R.	M. p.	Literature.
4-Diethylamino-2-butylamino *	262°	Magidson, *loc. cit.*; m. p. 265°.
6-Diethylamino-2-hexylamino	112	Kritchewski, *J. Microbiol. U.S.S.R.*, 1935, **14**, 642; m. p. 114°.
2-Diethylaminoethylamino	258—259	Breslow, *loc. cit.*; m. p. 257—259°.
3-Diethylaminopropylamino	249—251	,, ,, m. p. 254—255°.
4-Diethylaminobutylamino †	246—249	Magidson, *loc. cit.*; m. p. 246—248°.
5-Diethylaminoamylamino	266—268	Breslow, ,, m. p. 266—267°.
6-Diethylaminohexylamino	250—253	,, ,, m. p. 253—255°

* Free base, m. p. 80°. † Hydrate.

Polarography.—The above compounds were examined polarographically over a range of concentrations in supporting electrolytes buffered to various pH values. The buffers were 0·05M. and were prepared after Sörensen : pH 2 and pH 4, citrate–hydrochloric acid ; pH 5·5 and pH 7·3, phosphate ; pH 9, glycine–sodium hydroxide.

Breyer, Buchanan, and Duewell (*J.*, 1944, 360) found that 5-aminoacridine is reduced in two steps of approximately equal height at the dropping-mercury electrode. We find similar steps with our acridines, all of which are derivatives of 5-aminoacridine. The half-wave potentials and diffusion currents of the four Mepacrine homologues (I), at a concentration of 10^{-4}M. in various buffered supporting electrolytes, are given in Table II. The half-wave potentials of the homologues of the straight-chain series (II) vary in a similar manner, and their values for a drug concentration of 10^{-4}M. in supporting electrolytes of pH 7·3 are given in Table III.

TABLE II.

Mepacrine Homologues (I).

The diffusion currents were measured in microamps., and the half-wave potentials in volts. All the potentials are negative, and were measured relative to the saturated calomel electrode.

		pH 2.		pH 4.		pH 5·5.		pH 7·3.		pH 9.	
		1st step.	2nd step.	1st step.	2nd step.	1st step.	2nd step.	1st step.	2nd step.	1st step.	2nd step.
$x = 1$	$E_{\frac{1}{2}}$	0·74	—	0·78	1·18	0·84	1·20	0·86	1·21	0·85	1·09
	I_d	0·26	—	0·26	0·26	0·20	0·16	0·16	0·11	0·04	0·04
$x = 2$	$E_{\frac{1}{2}}$	0·74	—	0·80	1·18	0·91	1·20	0·94	1·21	0·93	1·09
	I_d	0·23	—	0·22	0·22	0·21	0·19	0·19	0·18	0·19	0·20
$x = 3$	$E_{\frac{1}{2}}$	0·74	—	0·80	1·18	0·93	1·20	0·97	1·21	0·94	1·09
	I_d	0·23	—	0·22	0·20	0·20	0·12	0·18	0·11	0·18	0·12
$x = 4$	$E_{\frac{1}{2}}$	0·74	—	0·80	1·18	0·93	1·20	0·97	1·21	0·94	1·09
	I_d	0·21	—	0·19	0·15	0·19	0·13	0·18	0·12	0·16	0·12

At pH 2 the hydrogen discharge wave overlaps the second reduction steps of these acridines in all cases.

TABLE III.

2-Chloro-5-R-7-methoxyacridines (II).

	50% EtOH–H_2O.		H_2O.	$E_{\frac{1}{2}}$.	
R.	pK_{b_1}.	pK_{b_2}.	pK_{b_2}.	1st step.	2nd step.
$Et_2N{\cdot}CH_2{\cdot}CHMe$–	6·51	8·32	7·31	0·86	1·21
$Et_2N{\cdot}[CH_2]_2{\cdot}CHMe$–	5·90	7·65	6·80	0·94	1·21
$Et_2N{\cdot}[CH_2]_3{\cdot}CHMe$–	5·11	7·13	6·47	0·97	1·21
$Et_2N{\cdot}[CH_2]_4{\cdot}CHMe$–	4·52	6·99	6·26	0·97	1·21
$Et_2N{\cdot}[CH_2]_2$–	6·01	7·84	6·95	0·84	1·07
$Et_2N{\cdot}[CH_2]_3$–	5·50	7·00	6·41	0·93	1·19
$Et_2N{\cdot}[CH_2]_4$–	5·04	6·64	6·14	0·94	1·19
$Et_2N[CH_2]_5$–	4·90	6·47	6·00	0·94	1·19
$Et_2N{\cdot}[CH_2]_6$–	4·66	6·43	5·98	0·94	1·19
$Et_2N{\cdot}[CH_2]_7$–	4·44	6·27	5·77	0·94	1·19
5-(3-Diethylaminopropylamino)acridine	4·61	6·26	5·46	0·97	1·20

By applying Ilkovic's equation, *viz.* :

$$I_d = 605\, nD^{1/2}Cm^{2/3}t^{1/6}$$

it is found that only one electron is taken up at each step, indicating that the first product of reduction is a free radical. Thus, for Mepacrine itself, in a phosphate buffer of pH 7·3, at 18°, we have C, the concentration of Mepacrine in millimoles/l. = 0·0993, D, the diffusion coefficient = 4·11 cm.^{2}/sec., m, the rate of flow of mercury = 1·36 mg./sec., and t, the drop time = 2·07 sec.

For the first step, I_d, the diffusion current = 0·185 μa. ; hence, n = 1·065 electrons.

For the second step, I_d = 0·115 μa. ; hence n = 0·705 electron.

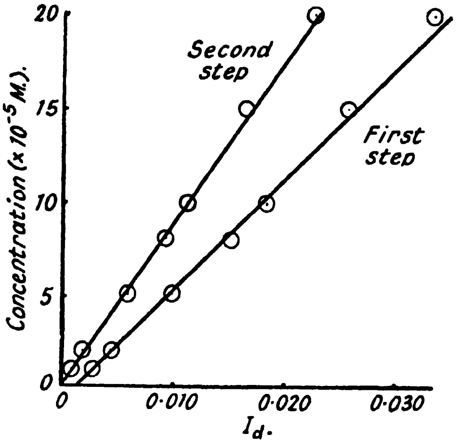
The diffusion coefficient, D, was calculated from Nernst's equation, $D = RT\Lambda_0/nF^2$. An approx. value of Λ_0 for Mepacrine was obtained by measuring the equivalent conductance of 10^{-3}M-Mepacrine dihydrochloride (54·7 mhos/cm.^{2}), and by multiplying this quantity by the ratio $\Lambda_0/\Lambda_{10^{-3}\text{M}}$. for barium nitrate, a salt of the same valency type.

It was further found that there is a linear relation between the concentration of the acridine drug and the diffusion current to which it gives rise in the polarographic cell, for both steps of the reduction process over the concentration range 10^{-5} to 2×10^{-4}M. For the case of Mepacrine itself in buffered supporting electrolytes of pH 7·3, the results obtained are given in the table below (diffusion currents in microamps.).

Concentration, 10^{-5}M.	1	2	5	8	10	15	20
I_d, 1st step	0·029	0·044	0·104	0·153	0·185	0·260	0·329
I_d, 2nd step	0·010	0·020	0·060	0·093	0·114	0·165	0·224

The gradient of the line connecting concentration with the diffusion current of the first step (1·750 mg. cm.^{2}/sec.) is much closer to the theoretical value (1·705) calculated from the Ilkovic equation than is that of the second step (1·250) (see Fig. 1). In the region where there is concentration–diffusion current proportionality, the current–voltage reduction curves obtained with the polarograph may be analysed by plotting log $I/(I_d - I)$ (where I is the current at chosen, successive points on the curve) against the applied E.M.F. Such an analysis of the waves given by Mepacrine at a concentration of 10^{-4}M., in a buffer supporting electrolyte of pH 7·3, gave a linear plot for both steps of the reduction. The plot obtained from the first wave again gave a gradient (57·6 mv.) closer to the theoretical (59·1 mv.) than that obtained by the analysis of the second wave (43·8 mv.) (see Figs. 2 and 3).

Fig. 1.



pH *Titrations.*—Mepacrine, and all the members of the two series of acridine antimalarials here dealt with, are di-acid bases. The second dissociation constant of any of these compounds can be determined by titrating an aqueous solution of the dihydrochloride with standard alkali, the pH being measured after each addition. Owing to the precipitation of free base after the addition of one equivalent of alkali, the first dissociation constant cannot be discovered in this way, as Christophers (*Ann. Trop. Med. Parasitol.*, 1937, **31**, 43) found in the case of Mepacrine. However, the free base is quite soluble in 50% aqueous-ethanolic solution and in this medium comparative values of both dissociation constants can be found by pH titrations. In this work N-sodium hydroxide was added from a microburette to 100 c.c. of M/100-solutions of the dihydrochlorides of each homologue, the pH being found by means of a glass electrode and Cambridge pH meter after each addition of alkali. No correction was applied for sodium-ion error as comparative values of the dissociation constants were all that this enquiry demanded. The results obtained are listed in Table III, together with the values of the half-wave potentials (reduction potentials), measured at a concentration of 10^{-4}M., in buffered supporting electrolytes of pH 7·3, at 18° ± 1°.

Fig. 2.

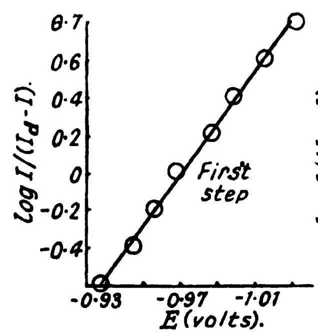
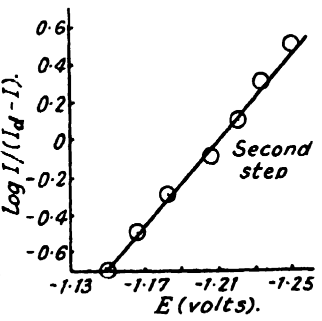


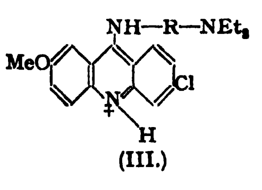
Fig. 3.



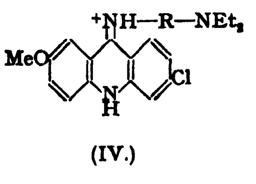
Discussion.

The polarographic measurements indicate that the first step in the reduction of Mepacrine and its analogues is probably thermodynamically reversible, since it conforms fairly closely to theoretical expectations, whilst the second would appear to be irreversible, as the deviations from theory are much larger. These views are consonant with the hypothesis that a free radical is the product of the first step, and a 5 : 10-dihydroacridine derivative the product of the second, as the former would be labile and the latter more stable (Breyer *et al.*, *loc. cit.*).

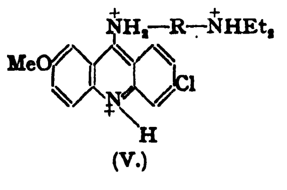
The increase in basicity with increasing length of side chain in these two series of acridine antimalarials may be ascribed to a decreasing field effect, though it is not possible to interpret this effect quantitatively in the terms used by Schwarzenbach (*Helv. Chem. Acta*, 1933, **16**, 522) for the symmetrical diamines, as the ionising powers of the two basic centres in these acridine derivatives cannot be taken as identical; further it is not possible to assign a precise location to the charge on the acridine nucleus, since the cation is probably a resonance hybrid of the forms (III) and (IV) :



(III.)



(IV.)



(V.)

In the first member of each series the tertiary nitrogen atom of the side chain is separated by only two carbon atoms from the secondary nitrogen atom at position 5 of the acridine nucleus, and thus an inductive effect down the side chain may discourage the formation of the quinonoid structure (IV), compelling the nitrogen atom at position 10 to carry a greater share of the positive charge. The lowering of the electron density round the nuclear nitrogen atom would then account for the observed lower basicity and greater ease of reduction in the first member of the series. The inductive effects of the chloro- and methoxy-substituents also decrease the basicity and enhance the cationoid activity of these compounds, as 5-(3-diethylaminopropylamino)acridine possesses a greater basicity and lower reduction potentials than the corresponding 2-chloro-7-methoxy-derivative.

In strongly acid media there is the possibility of tri-acid salt formation, as there are three basic centres in these acridine antimalarials. Christophers (*loc. cit.*) has shown that the possible third dissociation constant in Mepacrine must be greater than pK_b 11, though it is well known that Mepacrine salts, when crystallised from acid solution, contain more than two equivalents of acid, the excess being tenaciously held. If the third dissociation constant of these 5-diaminoacridines lies between pK_b 11 and 12, the tri-acid salt will predominate in buffer solutions of pH 2. Since the resonance postulated above is impossible in the tri-acid cation (V), the electron densities round the nuclear nitrogen atom in all of the homologues should be the same; the electron densities should be smaller than at other pH values where resonance " spreads " the positive charge in the di-acid cation, which might account for the fact that the half-wave potentials of the homologues are identical at pH 2, and lower than at other pH values.

The antimalarial activity of these 5-diaminoacridines reaches a maximum in both series when four carbon atoms separate the nitrogen atoms of the side chain (Kritchevski, *loc. cit.*; Magidson, *loc. cit.*). However, neither the reduction potentials nor the basicities show a maximum or minimum at this point in the series. With antimalarial drugs a simple relation between the values of some prescribed physico-chemical property and biological efficacy is hardly to be expected. In practice the drug must traverse the cellular tissue of the host and perhaps that of the parasite in order to interfere with some enzyme system or systems within the latter organism, and quite different factors might determine transfer from those that determine efficacy at the site of action. It was decided therefore to investigate those physico-chemical properties of acridine antimalarials that might influence their transit through biological material. This work will be described and discussed in a subsequent communication.

DYSON PERRINS LABORATORY, OXFORD.
MUSEUM OF THE HISTORY OF SCIENCE, OXFORD.
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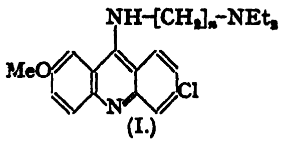
77. *Some Physico-chemical Properties of Acridine Antimalarials, with Reference to their Biological Action. Part II. Lipoid Partition Coefficients, Surface Activities, and Protein Affinities.*

By D. LL. HAMMICK and S. F. MASON.

The partition coefficients of a homologous series of acridine antimalarials between vegetable oil and aqueous buffers have been measured, and have been found to be related to the basic dissociation constants of the compounds. In aqueous solution these acridine derivatives are surface-active, and the lowering of the surface tension that they produce has been determined over a range of concentrations. The relative affinities of these compounds for the protein of egg albumin have also been determined.

ATTEMPTS have been made (preceding paper) to correlate the relative antimalarial activities of six members ($n = 2$—7) of a homologous series of acridine drugs (I) with their basicities and reduction potentials, but no definite relation has been observed. These physico-chemical properties were selected as a result of general considerations as to the nature of the action of acridine antimalarials on isolated enzyme systems, and on cultures of bacteria and the malaria parasite. In these cases the drug acts on biological systems isolated from their environment or host, whereas *in vivo* a drug must be able to permeate through the cellular material of the host and perhaps that of the parasite in order to be effective at some site of action within the parasite. Thus the relative permeabilities of a structurally similar series of antimalarial drugs may affect the antimalarial activities as determined in practice. The permeability of a drug through organic material is presumably dependent on physico-chemical factors, such as the solubility of the drug, its surface activity, lipoid partition coefficient, affinity for various proteins, and it was thought that the permeability of a given type of drug might possibly be optimum for certain values of these properties.



(I.)

The partition coefficients of six acridine antimalarials (I; n = 2—7) between vegetable oil and aqueous buffer solutions of pH 7·3 have been measured, as well as their surface activities and their relative affinities for the protein of egg albumin, both in M/20-phosphate buffers of pH 7·3 (the pH of blood).

EXPERIMENTAL.

Partition Coefficients.—Five standard solutions of the dihydrochloride of compound, covering the concentration range 10^{-4} to 10^{-3} M., were made up in M/20-phosphate buffer of pH 7·3. Each solution was divided into two parts: one was retained as a colorimetric comparator, whilst the other was shaken mechanically for 4 hours with such a volume of acid-free castor oil * as would extract between one-third and two-thirds of the acridine derivative (as indicated by preliminary experiments). The emulsion obtained was centrifuged, and the aqueous layer was then compared colorimetrically with the control solution. The latter was diluted to approx. the concentration of the extracted solution, and the comparison was repeated to guard against deviations from Beer's law. No deviations were detected, though the yellow acridine solutions did not permit of great accuracy in colorimetric comparison. Consequently the results are accurate only to within ±10%. Within these limits it was found that the ratio of the concentration of the compound in the lipoid phase to the concentration in the extracted aqueous phase was constant for each derivative over the concentration range studied. This ratio was then taken to be the partition coefficient of the compound between vegetable oil and aqueous buffer solution of pH 7·3, the values obtained being listed in the table below.

FIG. 1.

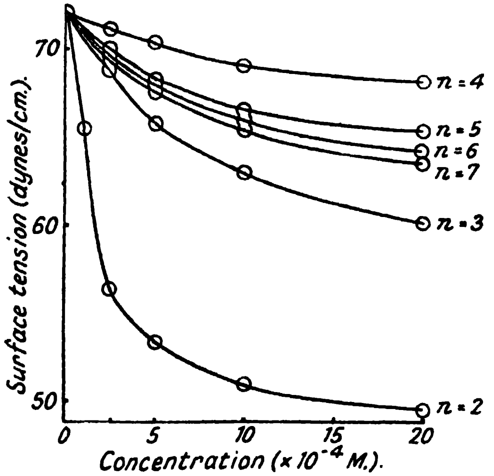
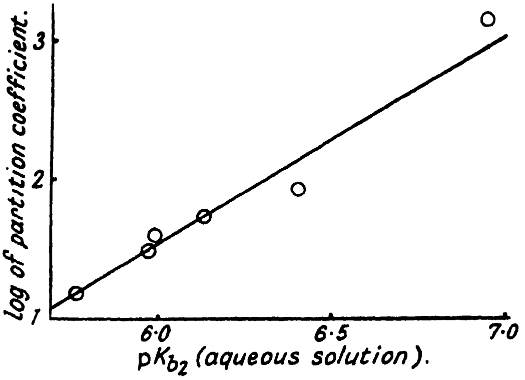


FIG. 2.



Surface Activities.—The surface tensions of solutions of each of the prepared acridine derivatives in M/20-phosphate buffer of pH 7·3 were measured by the drop-weight method, using a stalagmometer, over the concentration range 5×10^{-4} to 2×10^{-3} M. The stalagmometer was standardised with distilled water and with the phosphate buffer, by weighing in each case ten drops that had been allowed to fall from the orifice during about a minute. The weighings were repeated several times for reproducibility, the rate of flow of liquid being maintained at a constant value throughout the measurements by means of a capillary air leak. Measurements were then carried out with the solutions of various concentrations prepared from each of the derivatives, the weight of ten drops being determined several times. The surface tension of such solutions is proportional to the weight of the drops they form at a clean orifice, and thus the tensions may be evaluated from the known surface tension of a standard, such as distilled water. The results obtained are considered to be accurate to within about ±1% and are listed in the table and Fig. 1. They are perhaps less relevant to the purposes of this enquiry than the lipoid partition coefficients and protein affinites of the compounds, as there are not likely to be many air–water interfaces in the host–parasite system, and surface activities at such interfaces bear no necessary relation to activities at other interphase boundaries, such as those between lipoid and water, which are biologically more significant.

Protein Affinities.—Perhaps the most accurate and significant measure of drug–protein affinity is afforded by dialysis experiments (Davis, *Science*, 1942, **95**, 78). A membrane, such as Cellophane, separating isotonic solutions of protein and drug, permits the diffusion of a crystalloid drug, but not of a colloidal protein. At equilibrium there is a greater concentration of drug in the protein solution than in the aqueous solution, the excess affording a measure of the drug–protein affinity. A more convenient method is the precipitation of protein from an aqueous buffer solution with alcohol in the presence of the drug (Wormall and Dewey, *Biochem. J.*, 1946, **40**, 119). The relative amount of the drug carried down with the protein may then be taken to be a measure of the drug-protein affinity.

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* This work was carried out during the war when castor oil was the only vegetable oil available to the authors.

Both of these methods have been tried with one of the acridine homologues ($n = 4$) at six different concentrations over the range 5×10^{-5} to 2×10^{-3} M. in M/20-phosphate buffers of pH 7·3. In the dialysis experiments 20 c.c. of the buffered acridine solution were placed in a short boiling-tube fitted with a cork through which passed a piece of glass tubing closed at the lower end by a Cellophane membrane and at the upper end by a rubber bung. Into this tubing were pipetted 5 c.c. of an isotonic solution containing 5% by weight of crystalline egg albumin in a buffer of pH 7·3. The dialysis tubes were then kept in a refrigerator for two weeks, after which the experimental acridine drug solutions were compared colorimetrically with control solutions.

In the alcohol-precipitation experiments 5 c.c. of the same protein solution were added to 5 c.c. of a standard acridine drug solution in phosphate buffer. After some 30 minutes, 10 c.c. of ethyl alcohol were added, and the precipitated protein was centrifuged. The supernatant aqueous-alcoholic solution was then compared colorimetrically with a control that had been appropriately diluted with phosphate buffer and alcohol.

By both methods it was found that the amount of drug taken up by the protein was directly proportional to the drug concentration in the buffer solution up to concentrations of 5×10^{-4} M. under the conditions described above. The proportionality factors were very nearly the same in both cases, and were taken as measures of the drug–protein affinity. The protein affinities of the other members of the homologous series were then determined by the alcohol-precipitation method, as this was the more convenient. The partition of each derivative between protein and aqueous buffer was measured under comparable conditions by the means described above, at four concentrations over the range 5×10^{-5} to 5×10^{-4} M. where direct proportionality between the amount of drug taken up by the protein and the drug concentration in the residual solution had been observed. The ratio of these two quantities was then taken as the protein affinity of the compound under the given experimental conditions, and the values obtained were referred to the protein affinity of the homologue ($n = 2$) taken as unity. The results obtained are listed in the table. They are accurate only to within ±10%, the limiting factor being the sensitivity of the eye in the comparison of yellow acridine solutions.

2-*Chloro*-5-(ω-*diethylaminoalkylamino*)-7-*methoxyacridine* (I).

n.	Partition coeffs. between vegetable oil and buffer of pH 7·3.	Relative distribution factors between albumin and buffer of pH 7·3.	Lowering of the surface tension of buffer of pH 7·3 in dynes/cm. at drug concn. 10^{-3} M.
2	1600	1·0	21·0
3	82	2·1	9·0
4	54	2·7	3·0
5	43	6·8	5·5
6	31	14	6·0
7	15	17	6·6
5-(3-Diethylaminopropylamino)acridine	22	15	6·4

DISCUSSION.

In general the lyophobic character of organic compounds tends to increase with chain length in a homologous series, but in the case of the acridine homologues studied in the present work this relation did not hold. This may possibly be ascribed to the fact that under the experimental conditions at which measurements of oil–water partition coefficients were made, *i.e.*, at pH 7·3, these 5-diaminoacridines exist in the form of univalent and bivalent cations, the ratio of the two forms being determined by the value of pK_{b_2} for aqueous solutions. A plot of the logarithms of the partition coefficients for the series against the values of pK_{b_2} ($-\log K_2$) for aqueous solutions (preceding paper) gives a straight line with a slope of 1·6 (Fig. 2), indicating an inverse proportionality of this power between the vegetable-oil partition coefficient and the second dissociation constant of this particular type of compound at pH 7·3.

The surface activities and protein affinities of the acridine homologues seem not to be related in any definite way with other physico-chemical properties or structural features of the series. However, the relative values of these properties do seem to be related to the biological activities of the compounds, and in a subsequent communication these possible relations are discussed.

DYSON PERRINS LABORATORY, OXFORD.
MUSEUM OF THE HISTORY OF SCIENCE, OXFORD.

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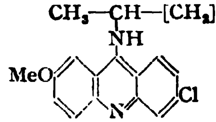
78. *Some Physico-chemical Properties of Acridine Antimalarials, with Reference to their Biological Action. Part III. The Correlation of Physico-chemical Properties with Biological Action.*

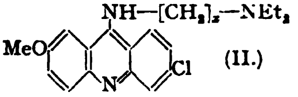
By S. F. Mason.

The degree to which members of two homologous series of acridine antimalarials (I and II) inhibit the enzyme system, diamine-oxidase, has been found to parallel the values of the reduction potentials of these compounds. No definite correlation between their antimalarial activities and their physico-chemical properties has been discovered, but an explanation of the order of their activities has been suggested, in terms of (*a*) the factors that possibly determine the permeability of these drugs through organic material, and (*b*) the equilibrium distribution of these compounds amongst the various organic phases within an organism, namely, their lipoid partition coefficents, surface activities, and relative protein affinities.

In Part I of this series (p. 345) an attempt was made to relate the antimalarial activities of two homologous series of acridine drugs (I and II) with their reduction potentials and basicities, but no relation was observed. This was ascribed to the complexity of antimalarial activity *in vivo*. A given drug must permeate through the cellular tissue of the host and perhaps of the parasite in order to interfere with some enzyme system, or systems, within the parasite, and *en route* may become distributed amongst the various phases, aqueous, lipoid, and protein, of both organisms, so that only a small concentration of the drug is present at the site of action. Thus the "antimalarial activities" of a series of drugs, as determined *in vivo*, may be a combination of their relative permeabilities and distribution factors, as well as of their relative potencies at the site of action.

(I.)





(II.)

It was thought that these two aspects of antimalarial activity might be separated for individual treatment, and in Part II of this series (preceding paper) the physico-chemical properties that might influence the permeability and distribution of these drugs in organic systems, namely, their lipoid partition coefficients, surface activities, and relative protein affinities, were measured for all members of series (II). The other factor contributing to the relative antimalarial activities of such a series of drugs, namely, their relative efficacies at the site of action, cannot be investigated physico-chemically at all fully as insufficient is known at present concerning the mode of action of 5-diaminoacridine antimalarials on the malaria parasite and other biological systems. However the physico-chemical properties chosen for investigation in Part I were selected by considering such knowledge as we have on this subject, the conclusion being reached that the reduction potentials and basicities of the acridine homologues (I and II) might be related to their activities on some simple biological system, such as an enzyme system, which would be free from the complication of the relative permeability and distribution factor.

Use was therefore made of the fact that 5-diaminoacridines inhibit the oxidation of diamines by diamine-oxidase. The concentrations required to inhibit this enzyme system to the extent of 50% were measured in the case of each of the acridine homologues (I and II), the values obtained being listed in Table I below.* This particular enzyme system was chosen because it might possibly be one of the vital activities of the malaria parasite that is suspended by acridine antimalarials analogous to Mepacrine (I; $n = 3$). Compounds of this type, to which all the derivatives used in the present work belong, are diamines, and thus might be expected to inhibit the utilisation of a structurally similar (diamine) metabolite by a biological organism. Furthermore Silverman and Evans (*J. Biol. Chem.*, 1944, **154**, 521) have shown that polyamines restore growth to cultures of bacteria inhibited by Mepacrine, and have demonstrated competitive antagonism between Mepacrine and polyamines in this connection.

This is not to suggest of course that the figures quoted for the inhibition of the diamine-oxidase system by our acridine derivatives provide a measure of their relative efficacies at the site of action within the malaria parasite, for there is no evidence as yet that the inhibition of diamine-oxidase is even a necessary, much less a sufficient, cause of antimalarial action.

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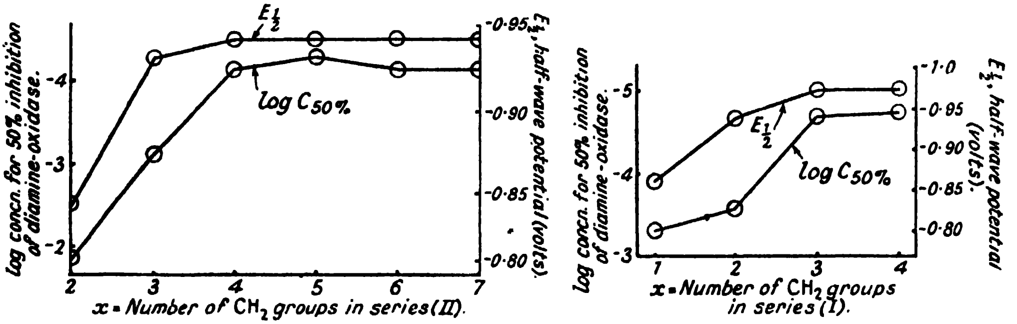
* The author is indebted to members of the Pharmacology Department, Oxford, for these measurements; notably to Dr. Duthie, who studied the four members of the branched-chain homologues (I), and to Dr. Blaschko, who investigated the six members of the straight-chain series (II).

TABLE I.

	x.	$E_{\frac{1}{2}}$, 1st step, v.	Concentration required to produce 50% inhibition of diamine oxidase, M.	$E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log C_{50\%\ \text{inhib.}}$ $n = 1$, v.	$n = 2$, v.
Series II.	2	$-0{\cdot}84$	$1{\cdot}45 \times 10^{-2}$	$-0{\cdot}73$	$-0{\cdot}79$
	3	$-0{\cdot}93$	$7{\cdot}5 \times 10^{-4}$	$-0{\cdot}75$	$-0{\cdot}84$
	4	$-0{\cdot}94$	$6{\cdot}5 \times 10^{-5}$	$-0{\cdot}70$	$-0{\cdot}82$
	5	$-0{\cdot}94$	5×10^{-5}	$-0{\cdot}69$	$-0{\cdot}82$
	6	$-0{\cdot}94$	$6{\cdot}5 \times 10^{-5}$	$-0{\cdot}70$	$-0{\cdot}82$
	7	$-0{\cdot}94$	$6{\cdot}5 \times 10^{-5}$	$-0{\cdot}70$	$-0{\cdot}82$
Series I.	1	$-0{\cdot}86$	5×10^{-4}	$-0{\cdot}67$	$-0{\cdot}75$
	2	$-0{\cdot}94$	3×10^{-4}	$-0{\cdot}74$	$-0{\cdot}84$
	3	$-0{\cdot}97$	2×10^{-5}	$-0{\cdot}70$	$-0{\cdot}84$
	4	$-0{\cdot}97$	$1{\cdot}7 \times 10^{-5}$	$-0{\cdot}70$	$-0{\cdot}84$

The first half-wave potentials (oxidation–reduction potentials) of these acridine homologues parallel to some degree the logarithms of the concentrations required to bring about 50% inhibition of the diamine-oxidase system (Fig. 1). Some connection between these two properties is perhaps to be expected since the system inhibited is concerned with oxidation, a process in which the oxidation–reduction characteristics of an inhibitory drug might be operative. The potential of an oxidation–reduction system, such as one of these acridine drugs present in both an oxidised and a reduced form, is governed by the equation :

FIG. 1.



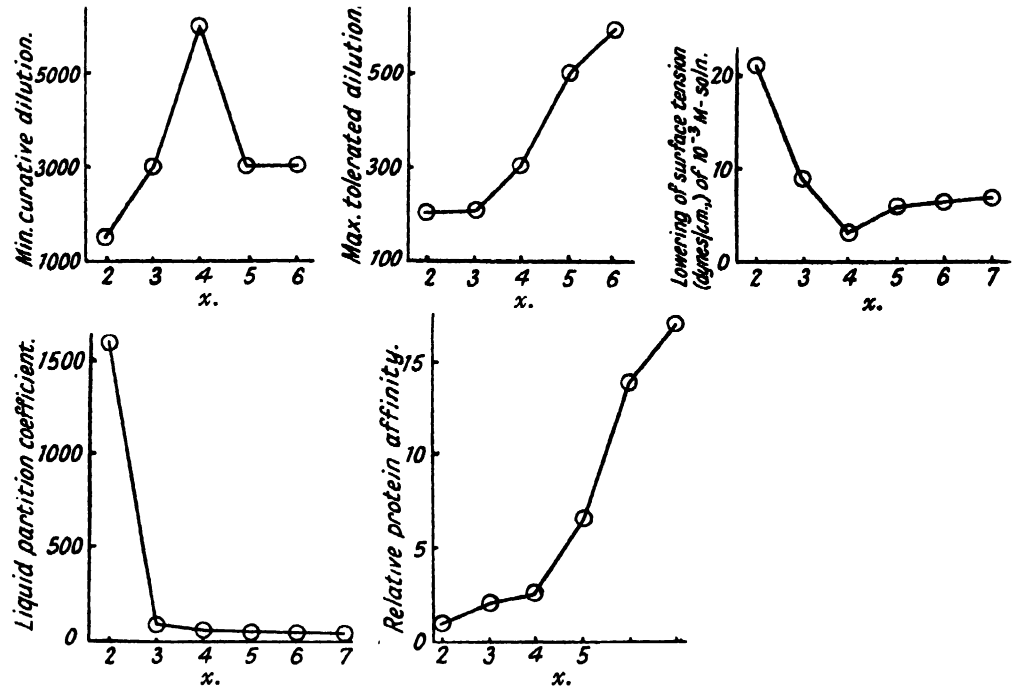
$$E = E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log \frac{C_{\text{red.}}}{C_{\text{oxid.}}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

which may be rearranged $$E - \frac{RT}{nF} \cdot \log C_{\text{oxid.}} = E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log C_{\text{red.}} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

It is found that the quantity, $E_{\frac{1}{2}} - \frac{RT}{nF} \cdot \log C_{50\%\ \text{inhib.}}$, has approximately the same value for each compound when $n = 1$, $n = 2$ electrons (Table I), the best constancy being obtained when $n = 1{\cdot}5$. This relation is curious, since it may be taken to imply that most of the drug used in inhibiting the diamine-oxidase system exists in the semi-reduced and fully reduced forms under conditions where the enzyme system is inhibited to the extent of 50%. It would also imply (equation 2) that the quantity, $E - \frac{RT}{nF} \cdot \log C_{\text{oxid.}}$, has approximately the same value for each compound in these conditions. Thus if it be assumed that a small constant quantity of the drug remains in the oxidised form, the determinant of a given degree of diamine-oxidase inhibition with these 5-diaminoacridines might be said to be the setting up of an oxidation–reduction system with a definite potential E, as lower half-wave potentials would be compensated by larger concentrations of the drug added to the enzyme system and passing into the reduced forms.

It is difficult to obtain a quantitative measure of antimalarial activity that is at all definitive, since numerical values obtained vary somewhat with the method of determination. However, the relative activities of the members of the two series (I and II) can be shown qualitatively, and it has long been accepted that the most active members of both series are those in which four carbon atoms separate the two nitrogen atoms of the side chain. The antimalarial data listed in Table II are taken from Magidson (*Ber.*, 1936, **69**, 396), the minimum curative dilution being a measure of the antimalarial activity of the derivative *in vivo*, and the maximum tolerated dilution a measure of its toxicity to the host; the physico-chemical data are taken from Part II of this series.

FIG. 2.



x = number of methylene groups in series (II).

TABLE II.

Compounds (II).

x.	Maximum tolerated dilution.	Minimum curative dilution.	Partition coeffs. between vegetable oil and buffer of pH 7·3.	Relative distribution factors between albumin and buffer of pH 7·3.	Lowering of the surface tension of buffer of pH 7·3 in dynes/cm.* at drug concn. 10^{-3} M.
2	200	1500	1600	1·0	21·0
3	200	3000	82	2·1	9·0
4	300	6000	54	2·7	3·0
5	500	3000	43	6·8	5·5
6	600	3000	31	14	6·0
7	*	—	15	17	6·6
5-(3-Diethylaminopropyl amino)acridine	†	—	22	15	6·4

* Tested through the courtesy of I.C.I. (Pharmaceuticals) Ltd. and found inactive at a dose of 4 mg. per 50 g. of body weight of host.

† Slightly active (Mietzsch, *Angew. Chem.*, 1934, **47**, 416).

Table II and the curves on Fig. 2 show that the antimalarial activities of the acridine homologues *in vivo* do not vary in the same way as their activities against the enzyme, diamine-oxidase, indicating that factors determining transfer and distribution in biological systems may be significant in determining their overall antimalarial action *in vivo*. It would appear (Table II) that the effectiveness of the 5-diaminoacridine type of antimalarial drug is enhanced by those properties that ensure a comparatively high equilibrium concentration of the drug in the aqueous phases of the host–parasite system. Homologues with high lipoid partition coefficients, large protein affinities, and, less significantly, high surface activities at air–water interfaces, are those which are less active against the malaria parasite. Thus the variation of these properties with the length of side chain may go some way towards explaining the variation of antimalarial activity from homologue to homologue, though a knowledge of their relative activities at the site of action within the parasite would be required to assess how important these physico-chemical properties are in determining the overall activity of the drugs *in vivo*. Like the diamine side-chains, the nuclear chloro- and methoxy-substituents of the drugs may play specific biochemical or stereochemical roles in transit and distribution throughout the host–parasite system, and in attacking the parasite, but their effects on the physico-chemical properties of the drugs are similar to variations produced by shortening the side chain, as can be seen by comparing 5-(3-diethylaminopropylamino)acridine with the corresponding 2-chloro-7-methoxy-derivative. The partition coefficient, surface activity, and protein affinity of the unsubstituted compound are quantitatively intermediate between those of the active ($x = 6$) and the inactive compound ($x = 7$), which is of interest in view of the fact that this unsubstituted compound shows slight antimalarial activity.

Correlation also exists between the toxicity of the compound to the host (the maximum tolerated dilution) and its relative protein affinity within the homologous series. This may perhaps be related to the vulnerability of complex functional proteins, such as the enzyme proteins. The protein affinities of these homologues probably vary from protein to protein, but it is possible that their relative affinities remain in the same order, unless specific stereochemical factors intervene. It is for this reason that the correlation is considered to be of possible significance.

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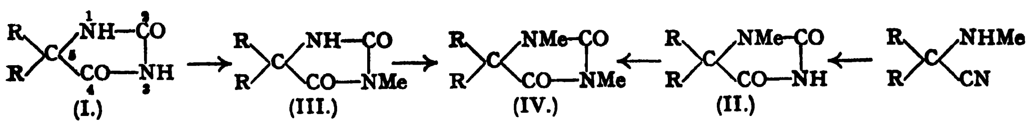
79. *Thiohydantoins. Part III. The* N- *and* S-*Methyl Derivatives of 5 : 5-Disubstituted Hydantoins and Their Mono- and Di-thio-analogues.*

By H. C. CARRINGTON and W. S. WARING.

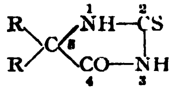
Examples have been provided of all the possible types of *N*- and *S*-methyl derivatives of 5 : 5-disubstituted hydantoins and their mono- and di-thio-analogues with the single exception of the 4-thio-2-methylthio-1-methyl derivatives. The experiments have been carried out in the 5 : 5-diphenyl and 5 : 5-pentamethylene series, and the results have been closely similar, but a few minor differences have been observed. The experimental methods used were simple, namely, methylation by methyl iodide, methyl sulphate, or diazomethane, replacement of oxygen by sulphur by the action of phosphorus pentasulphide, removal of methylthio-groups by acid hydrolysis, and replacement of sulphur by oxygen by the action of 2-aminoethanol followed by acid hydrolysis as described in Part II (Carrington, *J.*, 1947, 684).

ALTHOUGH a considerable amount of information on the alkylation of hydantoins is available, no systematic study of the various possible methyl derivatives of 5 : 5-disubstituted hydantoins and their thio-analogues has yet been made. It is well known that the alkali-soluble 5 : 5-disubstituted hydantoins (I) are readily methylated by the usual reagents to give the 3-methyl derivatives (III), which are converted by further, somewhat more drastic methylation into the 1 : 3-dimethyl derivatives (IV). The 1-methyl-5 : 5-disubstituted hydantoins (II) are not obtained by direct methylation, but are usually synthesised from the corresponding α-methylamino-nitriles by the action of cyanate, with subsequent hydrolysis. The 1-methyl derivatives, unlike the 3-methyl compounds, are soluble in alkali, and readily undergo further methylation to the 1 : 3-dimethyl derivatives. There appears to be no description of *O*-methylation occurring during the methylation of hydantoin derivatives.



When we consider the thiohydantoins, however, the formation of *S*-methyl derivatives must be taken into account, and the number of possible products is greatly increased. Thus with the 5 : 5-disubstituted-2-thiohydantoins (V) there are formally possible three monomethyl derivatives (VI—VIII) and three dimethyl derivatives (IX—XI). The corresponding 4-thiohydantoins (XXII) may lead to three possible monomethyl derivatives (XXIII—XXV) and two dimethyl derivatives (XXVI and XXVII), while the 2 : 4-dithiohydantoins (XII) may give rise to four monomethyl derivatives (XIII—XVI) and no less than five dimethyl derivatives (XVII—XXI).

The present experiments have set out to investigate how far these numerous possibilities can be realised in practice. They have been carried out, for the most part, with two series of compounds, the 5 : 5-diphenyl- and the 5 : 5-pentamethylene-hydantoins. In the first series the parent compound, 5 : 5-diphenylhydantoin itself, is well known, being widely used as a drug in the treatment of epilepsy. Several other members of this series are also known. Biltz, in his study of the reaction between benzil and urea and its derivatives, prepared 5 : 5-diphenyl-3-methylhydantoin (*Ber.*, 1908, **41**, 1386) and 5 : 5-diphenyl-1 : 3-dimethylhydantoin (*ibid.*, pp. 170, 1379). Similar experiments with thiourea and its derivatives led to 5 : 5-diphenyl-, 5 : 5-diphenyl-3-methyl-, and 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin, and it was also shown that methylation of the corresponding thio-compounds with methyl sulphate could give rise to the methylthio-derivatives 2-methylthio-4-keto-5 : 5-diphenyl- and 2-methylthio-4-keto-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (*idem*, *ibid.*, 1909, **42**, 1792). 5 : 5-Diphenyl-2 : 4-dithiohydantoin was prepared by Henze and Smith (*J. Amer. Chem. Soc.*, 1943, **65**, 1090) by the action of phosphorus trisulphide on the parent hydantoin. While the present work was in progress 5 : 5-diphenyl-1-methylhydantoin was prepared by Long, Miller, and Troutman (*ibid.*, 1948, **70**, 902) by a modification of the method usually used for 1-methylhydantoins.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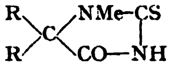
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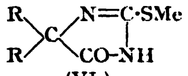
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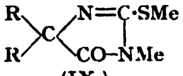
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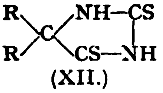
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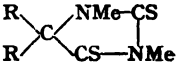
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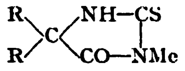
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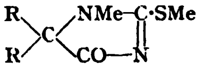
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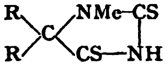
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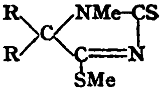
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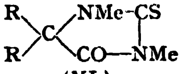
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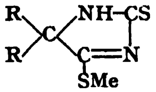
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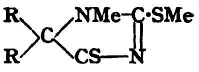
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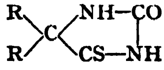
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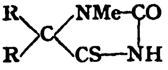
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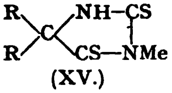
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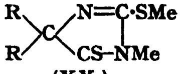
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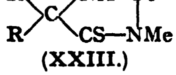
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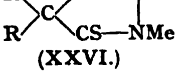
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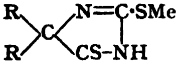
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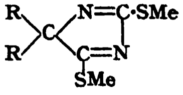
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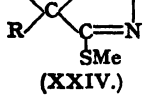
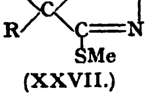

(XXIV.)


(XXVII.)

In the 5 : 5-pentamethylenehydantoin series the parent compound was prepared by Bucherer and Lieb (*J. pr. Chem.*, 1934, **141**, 5) during their pioneer development of new hydantoin syntheses. The corresponding 2-thio-, 4-thio-, and 2 : 4-dithio-hydantoins were described in the earlier papers of this series (Carrington, *J.*, 1947, 681, 684).

Comparatively few experimental procedures have been employed in the present study.

Methylations have been carried out using methyl iodide, methyl sulphate, and diazomethane. Phosphorus pentasulphide has been used for the replacement of oxygen by sulphur, and the reverse replacement of sulphur by oxygen has been accomplished by the action of 2-aminoethanol and subsequent hydrolysis of the 2-hydroxyethylimino-derivatives as described in Part II (*loc. cit.*). Alternatively, sulphur, where present in the form of methylthio-groups, has been removed by direct acid hydrolysis. By applying various permutations and combinations of these procedures it has been possible to synthesise nearly all the possible methyl derivatives.

Most of the experiments have been carried out in both the 5 : 5-diphenyl- and the 5 : 5-pentamethylene hydantoin series, and the results have been closely parallel. Only in a few cases have minor differences in behaviour been observed, and attention will be drawn to these. It is proposed to describe first the synthesis of some key reference compounds and then to discuss the more complicated methylations.

5 : 5-Diphenyl-1-methylhydantoin (II; R = Ph) was prepared both by the method of Long, Miller, and Troutman (*loc. cit.*) and by an alternative method which will be described later. Several other routes to the 5 : 5-diphenyl-1-methylhydantoin series were also investigated. α-Chlorodiphenylacetamide (Steinkopf, *Ber.*, 1908, **41**, 3593) was converted by methylamine in benzene into *α-methylaminodiphenylacetamide*, but attempts to cause this to react with carbon disulphide to give 5 : 5-diphenyl-1-methyl-2-thiohydantoin failed. Again, 5 : 5-diphenylhydantoin with benzyl chloride in aqueous-alcoholic alkali gave 5 : *5-diphenyl-*3*-benzylhydantoin*, which was further substituted by reaction with methyl sulphate to give 5 : *5-diphenyl-*1*-methyl-*3*-benzylhydantoin*, but attempts to remove the benzyl group by catalytic hydrogenation were unsuccessful. Treatment of 5 : 5-diphenyl-1-methylhydantoin with phosphorus pentasulphide in boiling tetralin gave 5 : *5-diphenyl-*1*-methyl-*2 : *4-dithiohydantoin* (XIII; R = Ph). 5 : 5-Diphenyl-3-methylhydantoin (III; R = Ph) gave similarly 5 : *5-diphenyl-*3*-methyl-*2 : *4-dithiohydantoin* (XV; R = Ph). 5 : *5-Diphenyl-*1 : *3-dimethyl-*2 : *4-dithiohydantoin* (XVII; R = Ph) was likewise prepared from 5 : 5-diphenyl-1 : 3-dimethylhydantoin (IV; R = Ph).

1-*Methyl-5* : *5-pentamethylenehydantoin* was prepared from α-methylaminohexahydrobenzonitrile in the usual way by treatment with cyanate followed by acid hydrolysis. 3-*Methyl-5* : *5-pentamethylenehydantoin* was prepared by methylation of 5 : 5-pentamethylenehydantoin in alkaline solution by methyl sulphate. Diazomethane may also be used. 1 : 3-*Dimethyl-5* : *5-pentamethylenehydantoin* was prepared from the 1-methyl-hydantoin in either of these ways. These three hydantoins were converted into the corresponding 2 : *4-dithiohydantoins* (XIII, XV, and XVII; RR = $<[CH_2]_5$, respectively).

These compounds, synthesised by unequivocal routes, form the basis on which the identification of most of the other derivatives depends.

The first methylation of a thiohydantoin studied in detail was the reaction of 5 : 5-diphenyl-2 : 4-dithiohydantoin with methyl sulphate. There were obtained an alkali-insoluble substance, and an alkali-soluble fraction which was clearly a mixture. The alkali-insoluble product was a colourless crystalline dimethyl derivative. When acid hydrolysis resulted in elimination of all the sulphur as methanethiol and formation of 5 : 5-diphenylhydantoin, it was clear that this derivative was 2 : *4-dimethylthio-5* : *5-diphenylglyoxaline* (XXI; R = Ph). The alkali-soluble fraction, on chromatographic separation, gave a pale yellow and a bright orange product; both were monomethyl derivatives and lost methanethiol on acid hydrolysis, giving monothiohydantoins. The pale yellow compound gave the known colourless 5 : 5-diphenyl-2-thiohydantoin (V; R = Ph), and was therefore identified as 2*-thio-*4*-methylthio-*5 : *5-diphenyl-*2 : *5-dihydroglyoxaline* (XIV; R = Ph). The isomeric bright orange derivative, by elimination, must therefore be the 4*-thio-*2*-methylthio*-compound (XVI; R = Ph), and the yellow monothiohydantoin obtained from it on hydrolysis must be 5 : *5-diphenyl-*4*-thiohydantoin* (XXII; R = Ph). It is of interest that the dimethyl derivative is formed in this methylation when only one equivalent of methyl sulphate, or even less, is used, and there is a corresponding recovery of unchanged 5 : 5-diphenyl-2 : 4-dithiohydantoin. It would appear that the monomethyl derivatives formed are more susceptible to further methylation than the unmethylated substance itself.

$$\begin{tikzcd}
\text{R = Ph. (XII)} \arrow[r, "Me_2SO_4", "\text{-NaOH}"'] & \text{(XIV)} \arrow[d, "HCl"] & + & \text{(XVI)} \arrow[d, "HCl"] & + & \text{(XXI)} \arrow[d, "HCl"] \\
& \text{(V)} & & \text{(XXII)} & & \text{(I)}
\end{tikzcd}$$

Some preliminary experiments on the methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin were described in Part II. There the main product isolated after removal of alkali-insoluble material and acidification of the remainder was identified as 5 : 5-pentamethylene-4-thiohydantoin. A more detailed study which has now been made showed that the alkali-insoluble product was mainly 2 : 4-*dimethylthio*-5 : 5-*pentamethyleneglyoxaline*, identified by acid hydrolysis to 5 : 5-pentamethylenehydantoin. This was probably accompanied by a little (XX; RR = $<[CH_2]_5$), for acid hydrolysis of the crude product gave also an alkali-insoluble substance later identified as 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII; RR = $<[CH_2]_5$). The alkali-soluble fraction was isolated by careful acidification with phosphoric acid, and on chromatographic separation gave three products, first, 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin, identical with that obtained by introduction of sulphur into the corresponding hydantoin, secondly, 4-*thio*-2-*methylthio*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (XVI; RR = $<[CH_2]_5$), identified by acid hydrolysis to 5 : 5-pentamethylene-4-thiohydantoin (XXII), and thirdly, the 2-*thio*-4-*methylthio*-isomer (XIV), which was identified both by acid hydrolysis to 5 : 5-pentamethylene-2-thiohydantoin (V; RR = $<[CH_2]_5$), and by reaction with 2-aminoethanol to give 4-2′-hydroxyethylimino-5 : 5-pentamethylene-2-thiohydantoin, identical with that described in Part II (*loc. cit.*). As in the 5 : 5-diphenylhydantoin series, there was also some unchanged starting material.

$$\begin{tikzcd}
RR = <[CH_2]_5. \ (XII) \arrow[r, "Me_2SO_4", "-NaOH"'] & (XIV) \arrow[d, "HCl"] & + & (XV) & + & (XVI) \arrow[d, "HCl"] & + & {[XX]} \arrow[d, "HCl"] & + & (XXI) \arrow[d, "HCl"] \\
& (V) & & (III) \arrow[u, "P_2S_5"'] & & (XXII) & & (XXIII) & & (I)
\end{tikzcd}$$

The main differences between the two series were, first, the slight tendency to *N*-methylation in the 3-position in the 5 : 5-pentamethylene series, and secondly, the variation in the proportion of the two monomethylthio-derivatives produced. In the 5 : 5-diphenyl series, the 4-methylthio-compound predominated, while in the 5 : 5-pentamethylene series there was more of the 2-methylthio-derivative. In the 5 : 5-pentamethylene series, the 4-thiohydantoin was the main alkali-soluble product when the acidification took place under such conditions as would bring about the hydrolysis of the very labile 2-methylthio-group.

The methylation of 5 : 5-diphenyl-2 : 4-dithiohydantoin with diazomethane gave rather different results. There were obtained two monomethyl and two dimethyl derivatives. The former were the 2-thio-4-methylthio-compound (XIV; R = Ph), the only product common to the methyl sulphate and diazomethane methylations, and 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV; R = Ph), identical with that obtained by introduction of sulphur into 5 : 5-diphenyl-3-methylhydantoin. The dimethyl derivatives were 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII; R = Ph), identical with that obtained from 5 : 5-diphenyl-1 : 3-dimethylhydantoin, and a new, pale yellow, crystalline compound, the structure of which was established as follows. It was identical with a dimethyl derivative obtained by the further methylation of 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV; R = Ph) either by methyl iodide or by diazomethane. Only two dimethyl derivatives could be derived by the further methylation of this compound. One of these was the 1 : 3-dimethyl compound (XVII; R = Ph) already identified, and the new compound must therefore be the other, 4-*thio*-2-*methylthio*-5 : 5-*diphenyl*-3-*methyl*-4 : 5-*dihydroglyoxaline* (XX; R = Ph). Confirmation of this structure was obtained by acid hydrolysis, methanethiol being evolved and a monomethyl monothio-derivative of diphenylhydantoin obtained which must clearly be 5 : 5-*diphenyl*-3-*methyl*-4-*thiohydantoin* (XXIII; R = Ph).

$$\begin{tikzcd}
R = Ph. \ (XII) \arrow[r, "CH_2N_2"] & (XIV) & + & (XV) \arrow[rrrr, bend left, "CH_2N_2 \text{ or } CH_3I"] & + & (XVII) & + & (XX) \arrow[d, "HCl"] \\
& & & (III) \arrow[u, "P_2S_5"'] & & (IV) \arrow[u, "P_2S_5"'] & & (XXIII)
\end{tikzcd}$$

Methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin by diazomethane gave as the main products 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV; RR = $<[CH_2]_5$) and 2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5 dihydroglyoxaline (XIV; RR = $<[CH_2]_5$). There was also an oily fraction of dimethyl derivatives which was not completely separated into its constituents, but which gave on acid hydrolysis 3-*methyl*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXIII; RR = $<[CH_2]_5$) thus indicating the presence of the 2-methylthio-3-methyl-4-thio-derivative, analogous to that obtained in the 5 : 5-diphenylhydantoin series.

The methylation of 5 : 5-diphenyl-2 : 4-dithiohydantoin in aqueous-alcoholic sodium hydroxide with one equivalent of methyl iodide gave a mixture of the 2-thio-4-methylthio-

(XIV; R = Ph) and the 2 : 4-dimethylthio-compound (XXI; R = Ph), with a recovery of some unchanged starting material. Methylation in alcoholic solution with an excess of methyl iodide and in the presence of sodium hydrogen carbonate gave the 2 : 4-dimethylthio-derivative, or, if the reaction was carried out at a higher temperature and without efficient stirring, *4-methylthio-2-keto-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XXIV; R = Ph). The structure of this compound was proved by its reaction with aqueous 2-aminoethanol to give *4-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* identical with that produced from 5 : 5-diphenyl-4-thiohydantoin by the same reagent. The formation of (XXIV) during this methylation clearly resulted from a partial hydrolysis of the preformed 2 : 4-dimethylthio-derivative, and this hydrolysis was, in fact, accomplished by careful treatment of 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline with 80% acetic acid.

In the methyl iodide methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin, loss of methanethiol occurred even more readily, and the only product isolated was *4-methylthio-2-keto-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XXIV; RR = $<[CH_2]_5$), identical with the product obtained by the action of methyl iodide on 5 : 5-pentamethylene-4-thiohydantoin. Its structure was confirmed (*a*) by conversion into 4-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, identical with that obtained from the 4-thiohydantoin by the same method (Carrington, *J.*, 1947, 684), and (*b*) by acid hydrolysis to 5 : 5-pentamethylenehydantoin.

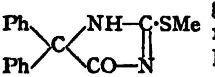
To complete the account of the methylation of the dithiohydantoin derivatives, it remains to describe experiments on the further methylation of various monomethyl derivatives. 5 : 5-Diphenyl-1-methyl-2 : 4-dithiohydantoin with methyl iodide or methyl sulphate gave mainly *4-methylthio-2-thio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII; R = Ph) (evidence for this structure will be discussed later), accompanied by a little 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin. The methylation of 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin with methyl iodide or diazomethane to give the 4-thio-2-methylthio-derivative has already been mentioned. 2-Thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline with diazomethane gave the 2 : 4-dimethylthio-derivative.

Methylation of 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin has been studied using all three reagents, and in all cases the 1 : 3-dimethyl- and the *4-methylthio-1-methyl*-compound (XVIII; RR = $<[CH_2]_5$) were obtained. The proportions of the two products, however, varied with the methylation procedure adopted. Thus, with diazomethane the former predominated, and with methyl iodide the latter, while with methyl sulphate approximately equal amounts of each were produced. With methyl iodide there was also formed, however, a very small amount of a yellow alkali-soluble monomethyl-monothio-derivative, which it seems can, by elimination, only be *1-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXV; RR = $<[CH_2]_5$), produced by hydrolysis of preformed 4-thio-2-methylthio-1-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline. This last type, the 4-thio-2-methylthio-1-methyl-derivative, remains the only class of methylated derivative which has not been exemplified in the present work.

3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin gave *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX; RR = $<[CH_2]_5$) on methylation either with methyl iodide or with diazomethane. The structure of this compound was proved in a similar way to that of the corresponding 5 : 5-diphenylhydantoin derivative, by the fact that acid hydrolysis liberated methanethiol, showing the second methyl group to be attached to sulphur, and gave as product 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII; RR = $<[CH_2]_5$). The presence of this dimethyl derivative had been deduced in the product of the diazomethane methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin by a similar hydrolysis, but its isolation in a state of purity was not accomplished in that case.

4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline with methyl iodide gave the 2 : 4-dimethylthio-derivative.

We must consider next experiments on the methylation of the monothiohydantoins. 5 : 5-Diphenyl-2-thiohydantoin (V; R = Ph), with methyl iodide in the usual way, gave 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI; R = Ph) (cf. Biltz, *loc. cit.*). This compound was also described by Cattelaine and Chabrier (*Bull. Soc. chim.*, 1947, 639) who gave it the formula (XXVIII), and stated that further methylation with methyl iodide gave 4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline, which could then be hydrolysed to 5 : 5-diphenyl-1-methylhydantoin. The present work, however, was in agreement with the observation of Biltz, and confirmed that the product of further methylation was the 3-methyl compound (IX; R = Ph), for on hydrolysis it gave 5 : 5-diphenyl-3-methylhydantoin.


(XXVIII.)

Methylation of 5 : 5-diphenyl-2-thiohydantoin with diazomethane gave three products. In addition to 4-keto-2-methylthio-5 : 5-diphenyl- and 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline described above, there was also produced 5 : 5-diphenyl-3-methyl-2-thiohydantoin (VII; R = Ph). The other possible structure for this compound, namely 5 : 5-diphenyl-1-methyl-2-thiohydantoin, was excluded by the synthesis of this latter compound by another route which will be described later.

$$\begin{tikzcd}
\text{R = Ph.} & \text{(VI)} & \text{(V)} \arrow[l, "\text{MeI}"'] \arrow[r, "\text{CH}_2\text{N}_2"] & \text{(VII) + (IX)} \arrow[r, "\text{HCl}"] & \text{(III)} \\
 & & & \text{(VI)} \arrow[u, "\text{MeI}"'] &
\end{tikzcd}$$

With methyl iodide 5 : 5-pentamethylene-2-thiohydantoin (V; RR = $<[\text{CH}_2]_5$) gave a result parallel to that just described for the 5 : 5-diphenyl series, 4-*keto*-2-*methylthio*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (VI; RR = $<[\text{CH}_2]_5$) being produced, the structure of which was proved by acid hydrolysis to methanethiol and 5 : 5-pentamethylenehydantoin. Diazomethane, however, gave only 3-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (VII; RR = $<[\text{CH}_2]_5$); the location of the methyl group in the 3-position was established, first, by conversion by phosphorus pentasulphide into 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin, and secondly, by further methylation with methyl iodide to give 4-*keto*-2-*methylthio*-3-*methyl*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (IX; RR = $<[\text{CH}_2]_5$) which was hydrolysed by acid to 3-methyl-5 : 5-pentamethylenehydantoin.

$$\begin{tikzcd}
\text{RR} = <[\text{CH}_2]_5. & \text{(VI)} \arrow[d, "\text{HCl}"] & \text{(V)} \arrow[l, "\text{MeI}"'] \arrow[r, "\text{CH}_2\text{N}_2"] & \text{(VII)} \arrow[r, "\text{MeI}"] \arrow[d, "\text{P}_2\text{S}_5"] & \text{(IX)} \arrow[d, "\text{HCl}"] \\
 & \text{(I)} & & \text{(XV)} & \text{(III)}
\end{tikzcd}$$

Comparatively few experiments have been carried out in the 4-thiohydantoin series. 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV; R = Ph) with methyl iodide gave the 1-*methyl* derivative (XXVII; R = Ph), which was readily hydrolysed to 5 : 5-diphenyl-1-methylhydantoin. This series of reactions was of interest in that it provided another means of entry into the series of 5 : 5-diphenyl-1-methyl derivatives, which is otherwise rather difficult of access.

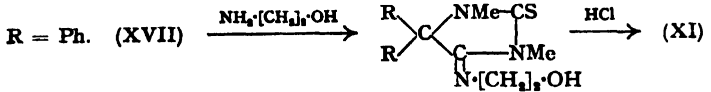
5 : 5-Pentamethylene-4-thiohydantoin, with methyl iodide, gave 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV; RR = $<[\text{CH}_2]_5$). When diazomethane was used, this product was accompanied by 3-methyl-5 : 5-pentamethylene-4-thiohydantoin, which had previously been obtained by the hydrolysis of the 2-methylthio-3-methyl-4-thio-derivative.

5 : 5-Diphenyl-3-methyl-4-thiohydantoin (XXIII; R = Ph), on treatment with methyl iodide, gave the 1 : 3-*dimethyl* derivative (XXVI; R = Ph). The establishment of the structure of this compound was of great value in settling the constitution of another derivative mentioned previously, the product obtained by the methylation of 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII; R = Ph). On acid hydrolysis, this last methylated product lost methanethiol and gave a 1-methyl-monothio-derivative, which could only be the 2- or 4-thio-compound. This was converted by diazomethane into a dimethyl-monothio-derivative, stable to acid and, therefore, with both methyl groups attached to nitrogen. As this substance was different from the 1 : 3-dimethyl-4-thiohydantoin described above, it clearly could only be 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI; R = Ph). The 1-methyl-monothio-derivative from which it was obtained must, therefore, be 5 : 5-*diphenyl*-1-*methyl*-2-*thiohydantoin* (VIII; R = Ph), and the product of methylation of the 1-methyl-2 : 4-dithiohydantoin was 2-*thio*-4-*methylthio*-5 : 5-*diphenyl*-1-*methyl*-2 : 5-*dihydroglyoxaline* (XVIII; R = Ph). Methylation of 5 : 5-diphenyl-1-methyl-2-thiohydantoin with methyl iodide gave 4-*keto*-2-*methylthio*-5 : 5-*diphenyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* (X; R = Ph), a compound of considerable interest, since it was the only example of a dimethyl derivative substituted in both the 1- and the 2-positions.

$$\begin{tikzcd}
\text{R = Ph.} & \text{(XXIII)} \arrow[d, "\text{MeI}"] & \text{(XIII)} \arrow[r, "\text{MeI}"] & \text{(XVIII)} \arrow[d, "\text{HCl}"] & \\
 & \text{(XXVI)} & \text{(XI)} & \text{(VIII)} \arrow[l, "\text{CH}_2\text{N}_2"'] \arrow[r, "\text{MeI}"] & \text{(X)}
\end{tikzcd}$$

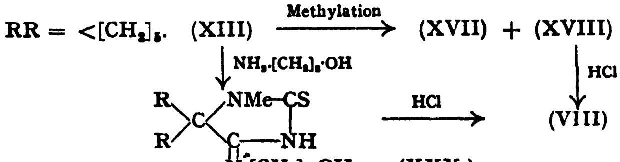
Further evidence of the structure of 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI;

R = Ph) has been obtained from its formation by another series of reactions. It was shown in Part II that when 2-aminoethanol reacted with a 5 : 5-disubstituted-2 : 4-dithiohydantoin the sulphur in the 4-position was preferentially replaced. It was further established that a 2-hydroxyethylimino-group was readily removed from the 4-position by acid hydrolysis, while in the 2-position it was unaffected by this treatment. The reaction of 2-aminoethanol with 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII; R = Ph) was therefore of considerable interest. First, it was not known whether reaction would occur at all, in view of the absence of a tautomerisable hydrogen atom : it was possible that the reaction would only take place with a $-C(SH)=N-$ grouping. Secondly, if reaction did take place, it was uncertain whether the preferential substitution in the 4-position would still occur, and whether the product would be hydrolysed by acid. In fact, the reaction followed the normal course, although it was slow, and the product, *4-2′-hydroxyethylimino-5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin* (XXIX; R = Ph) was readily hydrolysed by acid, giving 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI; R = Ph).



(XXIX.)

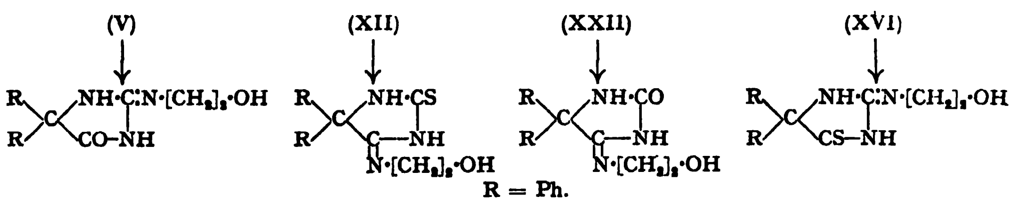
4-2′-Hydroxyethylimino-1-methyl-5 : 5-pentamethylene-2-thiohydantoin (XXX; RR = $<[CH_2]_5$) was obtained by the action of aqueous 2-aminoethanol on the 1-methyl-2 : 4-dithiohydantoin. On acid hydrolysis it gave *1-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VIII; RR = $<[CH_2]_5$), which was also produced by acid hydrolysis of 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), one of the products of methylation of the 1-methyl-2 : 4-dithiohydantoin.



(XXX.)

The action of diazomethane on 1-methyl-5 : 5-pentamethylene-2-thiohydantoin gave the 1 : *3-dimethyl* derivative (XI). From its method of formation this could only be the 1 : 3-dimethyl or the 2-methylthio-1-methyl derivative. As it was stable to acids, and therefore contained no methylthio-group, the former structure was correct.

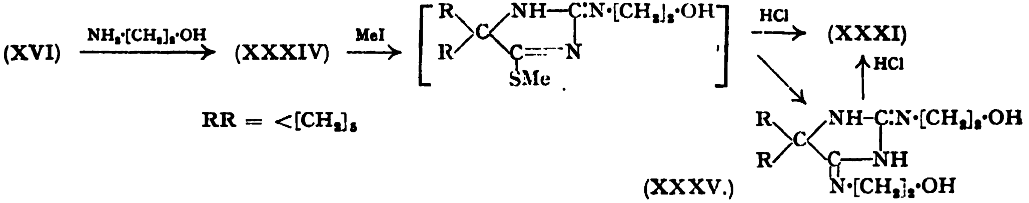
Methylthio-substituents in the hydantoin nucleus were replaced by 2-aminoethanol more readily than were the unmethylated thio-groups. Thus whereas 5 : 5-diphenyl-2 : 4-dithiohydantoin gave *4-2′-hydroxyethylimino-5 : 5-diphenyl-2-thiohydantoin* (XXXII; R = Ph), 5 : 5-diphenyl-4-thiohydantoin gave *4-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* (XXXIII; R = Ph), and 5 : 5-diphenyl-2-thiohydantoin gave *2-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* (XXXI; R = Ph), it was found that with 4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline reaction occurred preferentially in the 2-position, with formation of *2-2′-hydroxyethylimino-5 : 5-diphenyl-4-thiohydantoin* (XXXIV; R = Ph).



R = Ph.

(XXXI.) (XXXII.) (XXXIII.) (XXXIV.)

It might therefore be expected that the 2 : 4-dimethylthioglyoxalines would react with 2-aminoethanol with great ease to give derivatives with two 2-hydroxyethylimino-substituents. This, however, was not the case. These compounds were inert towards 2-aminoethanol, and when, under drastic conditions, reaction did occur, no identifiable products could be isolated. A hydantoin derivative with basic substituents in both the 2- and 4-positions has, however, been obtained by an indirect route. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI; RR = $<[CH_2]_5$) reacted readily with 2-aminoethanol to give *2-2′-hydroxyethylimino-5 : 5-pentamethylene-4-thiohydantoin* (XXXIV; RR = $<[CH_2]_5$). This could be methylated with methyl iodide in the usual way to give 2-2′-hydroxyethylimino-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline, which was not obtained analytically pure but was characterised by acid hydrolysis with loss of methanethiol to give 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin (XXXI; RR = $<[CH_2]_5$), identical with that described in Part II. The 4-methylthio-compound now reacted readily with a second molecule of 2-aminoethanol to give 2 : 4-*di*-(*2′-hydroxyethylimino*)-5 : *5-pentamethylenehydantoin* (XXXV; RR = $<[CH_2]_5$), which on acid hydrolysis was also converted into 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin.



Another interesting reaction was the removal of methylthio-groups in the reaction with phosphorus pentasulphide. Thus, an attempt was made to find a more convenient method for the preparation of 4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI; R = Ph) by the action of this reagent on the 4-keto-2-methylthio-compound, but the product obtained was 5 : 5-diphenyl-2 : 4-dithiohydantoin. A similar case was the preparation of 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin directly from 2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline. Such replacements have been described previously, for example, in the uracil series, by Elion and Hutchings (*J. Amer. Chem. Soc.*, 1947, **69**, 2138).

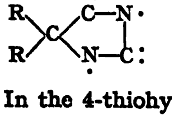
Of the twenty-seven possible types of 5 : 5-disubstituted hydantoins, their thio-analogues, and *N*- and *S*-methyl derivatives, we have thus been able to prepare representatives of all but one, namely, the 4-thio-2-methylthio-1-methyl compounds (XIX). The only case where it was possible to isolate a product with methyl groups in both the 1- and the 2-position was with 5 : 5-diphenyl-1-methyl-2-thiohydantoin, when methylation with methyl iodide occurred on the sulphur atom rather than at the 3- or 4-position.

It is not possible to formulate simple rules governing the methylation of these hydantoin derivatives, but a few general trends may be mentioned. Of the methylating agents used, methyl iodide tends to give most complete *S*-methylation. Diazomethane has the greatest tendency towards *N*-methylation, and methyl sulphate is intermediate. This is of course only to be expected, since diazomethane is used in ethereal solution, where the existence of –CS·NH– systems would be expected to be favoured. With the other methylating agents, the reaction was carried out in polar solvents in presence of sodium hydroxide, where –C(·SH)=N– systems should predominate.

There appears to be a general tendency for less *N*-methylation to occur in the 5 : 5-diphenyl series than in the 5 : 5-pentamethylene series.

An interesting contrast exists between the dithiohydantoins and the methylthio-derivatives in their behaviour towards acid. The 5 : 5-disubstituted 2 : 4-dithiohydantoins as a class are stable to acid hydrolysis, but, as described in Part II, 5 : 5-dimethyl-2 : 4-dithiohydantoin can be hydrolysed by acid to the corresponding 2-thio-derivative, the sulphur atom in position 4 being replaced by oxygen. When, however, 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline was submitted to a careful partial hydrolysis the 2-methylthio-group was removed first, leaving the 4-methylthio-group intact.

The ultra-violet absorption of the available pentamethylene derivatives has been measured in methanol solution. The hydantoins themselves show no specific absorption, but the thio-derivatives in general have characteristic bands. The structure of the dimethyl derivatives is fixed, and from their absorption spectra some deductions can be made of the probable structure of some of the unmethylated and monomethylated derivatives, where possibilities of tautomerism exist. In methanol solutions the compounds appear to exist wherever possible in the annexed form, with both the double bonds outside the ring. Thus in the dithio-series the compounds (XII), (XIII), and (XV) have spectra closely similar to that of (XVII) which must have a structure of the type indicated, and in the 2-thio-series the compounds (V), (VII), and (VIII) have spectra similar to that of (XI). In the 4-thiohydantoins there is no available compound in which this structure is obligatory,



but (XXII), (XXIII), and (XXV), with closely similar spectra, probably also exist in this form. No clear grounds appear to exist for the correlation of the structures of other members of the series with the fixed structures of (XVIII), (XX), and (XXI) on the basis of their absorption spectra in methanol solution.

EXPERIMENTAL.

In view of the large number of compounds involved and the fact that many of them are prepared by more than one experimental procedure, the table serves as an index to the Experimental section. References are there given for known compounds. Where alternative methods are described, the most favoured procedure is given first, followed by the others in order of preference. In the text below, cross-references given as " cf. A " etc. indicate identity established by mixed m. p. Absorption spectra were determined in methanol.

Formula no.	5 : 5-Diphenyl series.	5 : 5-Pentamethylene series.
I.	—	Bucherer and Lieb, *J. pr. Chem.*, 1934, **141**, 5.
II.	Long, Miller and Troutman, *J. Amer. Chem. Soc.*, 1948, **70**, 902; D.	G.
III.	Biltz, *Ber.*, 1908, **41**, 1386.	C, B.
IV.	Biltz, *Ber.*, 1908, **41**, 170, 1379.	C, B.
V.	Biltz, *Ber.*, 1909, **42**, 1792.	Carrington, *J.*, 1947, 684.
VI.	Biltz, *Ber.*, 1909, **42**, 1792; A, B.	A.
VII.	Biltz, *Ber.*, 1909, **42**, 1792; B.	B.
VIII.	D.	D.
IX.	Biltz, *Ber.*, 1909, **42**, 1792; A, B.	A.
X.	A.	—
XI.	Biltz, *Ber.*, 1909, **42**, 1792; F.	B.
XII.	Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090.	Carrington, *J.*, 1947, 681.
XIII.	E.	E.
XIV.	A, B, C.	B, C.
XV.	E, B.	E, B, C.
XVI.	C.	C.
XVII.	E, B, A, C.	E, B, C, A.
XVIII.	A.	A, C.
XIX.	—	—
XX.	A, B.	A, B, (C).
XXI.	A, C, B.	C, A.
XXII.	D.	Carrington, *J.*, 1947, 684.
XXIII.	D.	D, B.
XXIV.	D, A.	A, B.
XXV.	—	A.
XXVI.	A.	—
XXVII.	A, C.	—

(A) *Methylations with Methyl Iodide.*—The hydantoin (1 mol.) was suspended in methanol (or ethanol) (about 10 c.c. per g.) and aqueous sodium hydroxide (1 mol.; 12% solution) was added, whereupon the hydantoin dissolved. Alternatively, the hydantoin was dissolved in 1 equivalent of methanolic sodium hydroxide. Methyl iodide (1·1 mols.) was added and the mixture was set aside. The product usually crystallised, sometimes in a few minutes, sometimes overnight. When this failed to occur the alcohol was removed *in vacuo*, and the residue was washed with water, to remove sodium iodide, and purified by crystallisation.

In this way 5 : 5-diphenyl-2-thiohydantoin (V) gave 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI), colourless needles (from ethanol), m. p. 213° (90%) (Found : C, 67·75; H, 4·85; N, 10·1. Calc. for $C_{16}H_{14}ON_2S$: C, 68·1; H, 4·95; N, 9·95%). This (in ethanol) gave 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX), colourless needles (from ethanol), m. p. 175° (81%) (Found: C, 69·2; H, 5·4; N, 9·15. Calc. for $C_{17}H_{16}ON_2S$: C, 68·9; H, 5·4; N, 9·5%). 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV) (in ethanol) gave *2-keto-4-methylthio-5* : *5-diphenyl-*1*-methyl-2* : *5-dihydroglyoxaline* (XXVII), colourless needles (from ethanol), m. p. 229° (86%) (Found : C, 69·0; H, 5·65; N, 9·55. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). 5 : 5-Diphenyl-3-methyl-4-thiohydantoin (XXIII) (in ethanol) gave 5 : *5-diphenyl-*1 : *3-dimethyl-4-thiohydantoin* (XXVI), long cream-coloured prisms (from methanol), m. p. 211° (74%) (Found : C, 69·2; H, 5·4; N, 9·1. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). 5 : 5-Diphenyl-3-methyl-2 : 4-dithiohydantoin (XV) gave *4-thio-2-methylthio-5* : *5-diphenyl-3-methyl-4* : *5-dihydroglyoxaline* (XX), pale yellow plates (from methanol), m. p. 148° (92%) (Found : C, 65·2; H, 5·2; N, 8·95. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%). 5 : 5-Diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII) (in ethanol) gave *2-thio-4-methylthio-5* : *5-diphenyl-*1*-methyl-2* : *5-dihydroglyoxaline* (XVIII), pale yellow needles (from methanol), m. p. 205° (82%) (Found : C, 65·3; H, 5·15; N, 9·1. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%), accompanied by a very small amount of 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII) (cf. E).

5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) gave a mixture, which on chromatographic analysis from chloroform solution on alumina gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (32%; see below), *2-thio-4-methylthio-5* : *5-diphenyl-2* : *5-dihydroglyoxaline* (XIV), pale yellow plates (from ethanol), m. p. 256° (15%; this figure is probably low, owing to the difficulty of extracting this

very sparingly soluble substance from the alumina) (Found: C, 64·2; H, 4·5; N, 9·1. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), and a small amount of unchanged starting material.

5 : 5-Diphenyl-1-methyl-2-thiohydantoin (VIII) gave a gummy product, which after chromatographic treatment on alumina from a solution in 1 : 1 ether–chloroform gave 4-*keto*-2-*methylthio*-5 : 5-*diphenyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* (X), colourless needles (from methanol), m. p. 170° (20%) (Found: C, 68·7; H, 5·3; N, 9·7. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%).

5 : 5-Pentamethylene-2-thiohydantoin (V) gave 4-*keto*-2-*methylthio*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (VI), colourless needles (from aqueous methanol), m. p. 152—153° (70%) (Found: C, 54·3; H, 7·1; N, 13·8. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maximum, 2370 A.; ε = 11,100. 3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV) gave 4-*thio*-2-*methylthio*-3-*methyl*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (XX), colourless plates (from methanol), m. p. 63—64° (75%) (Found: C, 52·6; H, 6·8; N, 12·4. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maxima, 2500 and 2950 A.; ε = 8,900 and 11,800 respectively. 3-Methyl-5 : 5-pentamethylene-2-thiohydantoin (VII) gave 4-*keto*-2-*methylthio*-3-*methyl*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (IX), colourless prisms (from aqueous methanol), m. p. 62—63° (80%) (Found: C, 56·8; H, 7·5; N, 13·1. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·55; N, 13·2%); light absorption showed end absorption only. 5 : 5-Pentamethylene-4-thiohydantoin (XXII) gave 2-*keto*-4-*methylthio*-5 : 5-*pentamethylene*-2 : 5-*dihydroglyoxaline* (XXIV), colourless prisms (from a small quantity of methanol), m. p. 236° (42%) (Found: C, 54·3; H, 7·2; N, 14·0. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maximum, 2440 A.; ε = 9,820. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI) gave 2 : 4-dimethylthio-5 : 5-pentamethyleneglyoxaline (XXI), m. p. 48—49° (84%) (cf. C). 1-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) gave 2-*thio*-4-*methylthio*-1-*methyl*-5 : 5-*pentamethylene*-2 : 5-*dihydroglyoxaline* (XVIII), yellow prisms (from methanol), m. p. 148—149° (50%) (Found: C, 52·9; H, 7·0; N, 12·0. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maximum, 2880 A.; ε = 17,400. There was also found a small amount of 1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XVII), m. p. 126—127° (cf. E), and a few yellow needles of an alkali-soluble substance of m. p. 188—189°, which is believed to be 1-*methyl*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXV) (Found: C, 54·7; H, 7·1; N, 13·8. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%) (light absorption: Maxima, 2360 and 2850 A.; ε = 5,750 and 11,400, respectively). When the sodium salt of 5 : 5-pentamethylene-2 : 4-dithiohydantoin (XII) was treated with methyl iodide in methanol solution at room temperature, methanethiol was evolved; after removal of the solvent *in vacuo* the residue was washed with ether and water, and extracted with chloroform. Evaporation of the chloroform solution gave 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV), m. p. 234° (from methanol) (cf. above).

Other methylations with methyl iodide were carried out in alcoholic solution in presence of sodium hydrogen carbonate. 5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) (7·1 g.) in methanol (100 c.c.) was heated under reflux to 50° with efficient stirring for 5 hours with methyl iodide (10 g.) and sodium hydrogen carbonate (6 g.). After the mixture had been kept overnight the product crystallised, and was filtered off, washed with water, and dried, giving 2 : 4-*dimethylthio*-5 : 5-*diphenylglyoxaline* (XXI), long colourless prisms (from methanol), m. p. 140° (88%) (Found: C, 65·3; H, 5·35; N, 8·6. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%) (cf. above). Under slightly more vigorous conditions and without efficient stirring, a different product was obtained. Thus, (XII) (7·1 g.) in methanol (100 c.c.) was heated under reflux at 60—70° with methyl iodide (8·5 g.) and sodium hydrogen carbonate (5 g.) for 6 hours without stirring. After cooling the crystalline product was filtered off to give 2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV), colourless prisms (from ethanol), m. p. 264° (32%) (cf. D).

(B) *Methylations with Diazomethane.*—The hydantoin was added to excess of an ethereal solution of diazomethane. In some cases a little methanol was added. The mixture was set aside overnight, and the product was isolated by removal of excess of diazomethane and ether by distillation.

5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) gave a complex mixture of products from which, by chromatographic separation of a chloroform solution on alumina, there were isolated: 4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (XX), m. p. 148° (42%) (cf. A), 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV), m. p. 206° (20%) (cf. E), 2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV), m. p. 256° (15%) (cf. A), and 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII), m. p. 167° (2%) (cf. E). The proportion of the mono- and di-methyl derivatives obtained probably depends upon the amount of diazomethane in excess. 2-Thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV) gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (40%) (cf. A). 5 : 5-Diphenyl-3-methyl-2 : 4-dithiohydantoin (XV) gave 4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (XX), m. p. 148° (75%) (cf. A). 5 : 5-Diphenyl-2-thiohydantoin (V) gave a mixture, separated by passage of its ethereal solution through an alumina column, into 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX), m. p. 175° (5%) (cf. A), 5 : 5-diphenyl-3-methyl-2-thiohydantoin (VII), colourless needles (from ethanol), m. p. 186° (25%) (Found: C, 68·1; H, 5·2; N, 10·0. Calc. for $C_{16}H_{14}ON_2S$: C, 68·1; H, 4·95; N, 9·95%), and 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI), m. p. 212° (7%) (cf. A).

5 : 5-Pentamethylenehydantoin (I) gave 3-methyl-5 : 5-pentamethylenehydantoin (III), m. p. 213° (93%) (cf. C). 1-Methyl-5 : 5-pentamethylenehydantoin (II) gave 1 : 3-dimethyl-5 : 5-pentamethylenehydantoin (IV), m. p. 68—69° (cf. C). 5 : 5-Pentamethylene-2-thiohydantoin gave 3-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (VII), colourless plates (from methanol), m. p. 174—175° (78%) (Found: C, 54·8; H, 7·1; N, 14·3. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maxima, 2320 and 2670 A.; ε = 9,360 and 18,000 respectively. 5 : 5-Pentamethylene-4-thiohydantoin (XXII) gave a mixture of 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV), m. p. 234° (50%) (cf. A), and 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII), m. p. 191° (25%) (cf. D). 1-Methyl-5 : 5-pentamethylene-2-thiohydantoin (VIII) gave 1 : 3-*dimethyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (XI), colourless jagged needles (from aqueous methanol), m. p. 118—119° (70%) (Found: C, 56·4; H, 7·5; N, 13·0. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·55; N, 13·2%); light

absorption: Maxima, 2380 and 2650 A., ε = 13,570 and 17,100 respectively. 5 : 5-Pentamethylene-2 : 4-dithiohydantoin (XII) gave a mixture of products. There separated from the reaction mixture *2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XIV), colourless needles (from methanol), m. p. 217—218° (26%) (Found: C, 50·7; H, 6·6; N, 12·7. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption: Maximum, 2820 A.; ε = 11,600. Inflexion, 3070 A., ε = 8,700. The residue, after removal of ether and excess of diazomethane, was triturated with light petroleum (b. p. 40—60°) to give 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV), m. p. 191—192° (46%) (cf. E). The light-petroleum washings, on evaporation, left an oil which was not purified but on acid hydrolysis lost methanethiol and gave 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII), m. p. 191° (9%) (cf. D); this indicated the presence of 4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX). Methylation of 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) with diazomethane gave 1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XVII), m. p. 126° (45%) (cf. E), and 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), m. p. 148—149° (5%) (cf. A). 3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV) gave 4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX), m. p. 63—64° (90%) (cf. A).

(C) *Methylations with Methyl Sulphate.*—5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) (15 g.) was dissolved in dilute aqueous sodium hydroxide (165 c.c.; 4%). To the stirred solution, methyl sulphate (9 g.) was added during 10 minutes, the temperature being kept below 20°. The mixture was stirred for a further 2 hours and was then filtered. The solid product, recrystallised from methanol, gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (25%) (cf. A). The alkaline filtrate was clarified with kieselguhr and then acidified with hydrochloric acid, and the product was extracted with chloroform. The dried chloroform solution was passed through an alumina column, affording 2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV), m. p. 256° (19%) (cf. A), and *4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline* (XVI), bright orange-yellow needles (from methanol), m. p. 211° (13%) (Found: C, 64·3; H, 4·65; N, 9·1. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), which darkened on exposure to light.

In a similar manner 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII) gave a mixture from which there were obtained, by chromatographic separation from ether–chloroform (1 : 1) on alumina, 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII), m. p. 167° (12%) (cf. E), and 2-thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XVIII), m. p. 205° (30%) (cf. A).

Methyl sulphate (32 g.) was added during 5 minutes to a stirred solution of 5 : 5-pentamethylene-hydantoin (I) (34 g.) in aqueous sodium hydroxide (10 g. in 200 c.c.), the temperature being kept below 40°. After being stirred for a further 10 minutes the mixture was cooled and filtered, and the solid product was recrystallised from methanol, giving *3-methyl-5 : 5-pentamethylenehydantoin* (III), colourless needles, m. p. 212—213° (75%) (Found: C, 59·5; H, 7·8; N, 15·3. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

Similarly 1-methyl-5 : 5-pentamethylenehydantoin gave *1 : 3-dimethyl-5 : 5-pentamethylenehydantoin*, colourless prisms (from aqueous methanol), m. p. 68—69° (74%) (Found: C, 60·8; H, 8·2; N, 14·4. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2; N, 14·3%).

5 : 5-Pentamethylene-2 : 4-dithiohydantoin (XII) (48 g.) in aqueous sodium hydroxide (360 c.c.; 8%) was methylated by addition of methyl sulphate (36 g.) with stirring, during 20 minutes, temperature being kept at 5—10°. The mixture was stirred for a further 3 hours, the temperature being allowed to rise to 20°. The insoluble solid was filtered off and recrystallised from aqueous methanol, to give *2 : 4-dimethylthio-5 : 5-pentamethyleneglyoxaline* (XXI) as colourless needles, m. p. 48—49° (33%) (Found: C, 53·0; H, 7·1; N, 12·5. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maximum, 2570 A.; ε = 6,800. This substance was soluble in dilute hydrochloric acid and could be distilled *in vacuo* (b. p. 120°/0·3 mm.). The crude alkali-insoluble solid also appeared to contain some 4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX), for acid hydrolysis gave, in addition to 5 : 5-pentamethylenehydantoin (I), an alkali-insoluble product identified as 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII), m. p. 191° (cf. D). The alkaline filtrate from the methylation was acidified below 10° with phosphoric acid, and the solid was filtered off, washed with water, and dried. Chromatographic separation from chloroform solution on alumina gave as the main product *4-thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XVI), bright yellow needles (from aqueous methanol), m. p. 161° (30%) (Found: C, 50·6; H, 6·6; N, 13·4. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption: Maxima, 2550, 2970, and 3300 A.; ε = 7,880, 8,340, and 8,890 respectively. This compound darkened on exposure to light. It was accompanied by small quantities of 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV), m. p. 191—192° (cf. E), and 2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XIV), m. p. 217—218° (cf. B).

1-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII), methylated under similar conditions, gave a mixture which was separated chromatographically from chloroform solution on alumina into 1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XVII), m. p. 126° (29%) (cf. E), and 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), m. p. 148—149° (23%) (cf. A).

(D) *Hydrolysis of Methylthio-compounds.*—The methylthio-compound (5 g.) in 20% hydrochloric acid (20 c.c.) was heated under reflux for ½—4 hours. Methanethiol was evolved, and on cooling the product separated. In the 5 : 5-diphenyl series, where the starting materials were sparingly soluble, the hydrolysis was usually carried out in a mixture of 36% hydrochloric acid (20 c.c.) and ethanol (50 c.c.).

In this way 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI) gave 5 : 5-diphenylhydantoin (I), colourless crystals (from aqueous methanol), m. p. 300° (60%). The same product was obtained from 2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV) (65%). 2-Keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XXVII) gave 5 : 5-diphenyl-1-methylhydantoin (II), long colourless prisms (from aqueous methanol), m. p. 225° (94%) (Found: C, 72·3; H, 5·3; N, 11·2. Calc. for $C_{16}H_{14}O_2N_2$: C, 72·2; H, 5·25; N, 11·5%). The same product was obtained in almost theoretical yield from 4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline (X). 4-Keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX) gave 5 : 5-diphenyl-3-methylhydantoin (III) in almost theoretical yield. 4-Thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI) gave 5 : *5-diphenyl-4-thiohydantoin* (XXII), bright yellow prisms (from methanol), m. p. 273—274° (80%) (Found : C, 66·8; H, 4·6; N, 10·4. $C_{15}H_{12}ON_2S$ requires C, 67·2; H, 4·5; N, 10·45%). 2-Thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XVIII) gave 5 : *5-diphenyl-1-methyl-2-thiohydantoin* (VIII), cream needles (from aqueous ethanol), m. p. 215° (83%) (Found : C, 68·2; H, 4·95; N, 10·0. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%). 4-Thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (XX) gave 5 : *5-diphenyl-3-methyl-4-thiohydantoin* (XXIII), pale yellow needles (from aqueous methanol), m. p. 202° (82%) (Found : C, 68·2; H, 5·1; N, 9·95. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%).

2 : 4-Dimethylthio-5 : 5-pentamethyleneglyoxaline (XXI), 4-keto-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (VI), or 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV) gave 5 : 5-pentamethylenehydantoin (I), m. p. 217—218°, on acid hydrolysis. 4-Keto-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (IX) gave 3-methyl-5 : 5-pentamethylenehydantoin (III), m. p. 212° (47%). 2-Thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XIV) gave 5 : 5-pentamethylene-2-thiohydantoin (V), m. p. 190—191° (81%); light absorption : Maxima, 2240 and 2660 A.; ε = 9,910 and 20,300 respectively. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI) gave 5 : 5-pentamethylene-4-thiohydantoin (XXII), m. p. 240°; light absorption : Maxima, 2300 and 2780 A.; ε = 4,360 and 15,500 respectively. 4-Thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX) gave 3-*methyl*-5 : *5-pentamethylene-4-thiohydantoin* (XXII), almost colourless plates (from methanol), m. p. 190—191° (71%) (Found : C, 54·8; H, 6·9; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption : Maxima, 2290 and 2780 A.; ε = 5,300 and 15,100 respectively. 2-Thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII) gave in almost quantitative yield 1-*methyl*-5 : *5-pentamethylene-2-thiohydantoin* (VIII), colourless needles (from aqueous methanol), m. p. 153° (Found : C, 54·8; H, 7·2; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption : Maxima, 2300 and 2650 A.; ε = 7,450 and 12,750 respectively.

2 : 4-Dimethylthio-5 : 5-diphenylglyoxaline (XXI) (8 g.) was heated under reflux for ½ hour with glacial acetic acid (80 c.c.) and water (20 c.c.). Methanethiol was evolved. Water (200 c.c.) was added, the mixture was cooled, and the product was filtered off, washed with water, and recrystallised from ethanol, to give *2-keto-4-methylthio*-5 : *5-diphenyl*-2 : *5-dihydroglyoxaline* (XXIV), colourless prisms, m. p. 264° (64%) (Found : C, 67·7; H, 5·0; N, 9·5. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%).

(E) *Introduction of Sulphur.*—The hydantoin (10 g.) and phosphorus pentasulphide (10 g.) were suspended in tetralin (60 c.c.; more was occasionally required with sparingly soluble compounds), and boiled under reflux with efficient stirring for 1—1½ hours. The mixture was filtered hot. The product separated from the solution on cooling. It was filtered off, and purified by recrystallisation.

5 : 5-Diphenyl-2-thiohydantoin (V) gave 5 : 5-diphenyl-2 : 4-dithiohydantoin (XII), bright yellow prisms (from methanol), m. p. 268° (70%), also produced similarly from 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI). 5 : 5-Diphenyl-1-methylhydantoin (II) gave 5 : *5-diphenyl*-1-*methyl*-2 : 4-*dithiohydantoin* (XIII), lemon-yellow prisms (from methanol), m. p. 217° (82%) (Found : C, 64·8; H, 4·85; N, 9·25. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), also obtained from 2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XXVII). 5 : 5-Diphenyl-3-methylhydantoin (III) gave 5 : *5-diphenyl-3-methyl*-2 : 4-*dithiohydantoin* (XV), yellow prisms (from methanol), m. p. 206° (47%) (Found : C, 64·6; H, 4·75; N, 9·3. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%). 5 : 5-Diphenyl-1 : 3-dimethylhydantoin (IV) gave 5 : *5-diphenyl*-1 : 3-*dimethyl*-2 : 4-*dithiohydantoin* (XVII), yellow needles (from methanol), m. p. 167° (60%) (Found : C, 65·5; H, 5·3; N, 8·8. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%).

1-Methyl-5 : 5-pentamethylenehydantoin (II) gave 1-*methyl*-5 : *5-pentamethylene*-2 : 4-*dithiohydantoin* (XIII), yellow hexagonal plates (from aqueous methanol), m. p. 192—193° (60%) (Found : C, 50·2; H, 6·5; N, 13·25. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption : Maxima, 2250 and 2980 A.; ε = 7,430 and 26,200. 3-Methyl-5 : 5-pentamethylenehydantoin (III) gave 3-*methyl*-5 : *5-pentamethylene*-2 : 4-*dithiohydantoin* (XV), yellow prisms (from methanol), m. p. 191—192° (46%) (Found : C, 50·5; H, 6·8; N, 13·4. $C_{19}H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption : Maxima, 2250 and 2980 A.; ε = 6,690 and 29,100 respectively. This compound was also obtained similarly from 3-methyl-5 : 5-pentamethylene-2-thiohydantoin (VII). 1 : 3-Dimethyl-5 : 5-pentamethylenehydantoin (IV) gave 1 : 3-*dimethyl*-5 : *5-pentamethylene*-2 : 4-*dithiohydantoin* (XVII), long yellow needles (from ethanol), m. p. 126° (26%) (Found : C, 52·5; H, 7·2; N, 12·0. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption : Maxima, 2240 and 2980 A.; ε = 6,300 and 26,250 respectively.

(F) 2-*Aminoethanol Derivatives.*—5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) was boiled under reflux for ½ hour with 5 parts of 2-aminoethanol. Hydrogen sulphide was evolved, and after cooling the solid product was filtered off. Recrystallisation from ethanol gave 4-2′-*hydroxyethylimino*-5 : *5-diphenyl-2-thiohydantoin*, colourless crystals, m. p. 218° (60%) (Found : C, 63·8; H, 5·6; N, 13·0. $C_{17}H_{17}ON_3S,\frac{1}{2}H_2O$ requires C, 63·8; H, 5·95; N, 13·1%), obtained also from 2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV). In a similar manner 5 : 5-diphenyl-2-thiohydantoin (V), on refluxing for 3 hours with aqueous 2-aminoethanol, gave 2-2′-*hydroxyethylimino*-5 : *5-diphenylhydantoin*, colourless prisms (from dimethylformamide), m. p. 298° (Found : C, 68·9; H, 5·9; N, 14·3. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·75; N, 14·25%), also was obtained by the action of 2-aminoethanol on 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI). 4-Thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI) with aqueous 2-aminoethanol (15 minutes under reflux) gave 2-2′-*hydroxyethylimino*-5 : *5-diphenyl-4-thiohydantoin*, colourless crystals (from aqueous ethanol), m. p. 239° (Found : C, 66·0; H, 5·0; N, 13·3. $C_{17}H_{17}ON_3S$ requires C, 65·6; H, 5·45; N, 13·5%). 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV), on heating under reflux with aqueous 2-aminoethanol for 15 minutes, gave an almost quantitative yield of 4-2′-*hydroxyethylimino*-5 : *5-diphenylhydantoin*, colourless crystals (from ethanol), m. p. 249° (Found : C, 69·2; H, 5·7; N, 14·1. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·75; N, 14·25%). 5 : 5-Diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII), when heated under reflux with aqueous 2-aminoethanol for 4 hours, gave *4-2′-hydroxyethylimino-5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin*, colourless crystals (from aqueous ethanol), m. p. 158° (Found : C, 67·2; H, 6·2; N, 12·2. $C_{19}H_{21}ON_3S$ requires C, 67·2; H, 6·2; N, 12·4%). It was found difficult to complete this reaction, and in the isolation of the product it was best to extract it with excess of cold dilute hydrochloric acid, filter from unchanged starting material, and reprecipitate it with ammonia before crystallisation. This compound, on being heated under reflux for ½ hour with 50 parts of 20% hydrochloric acid, was hydrolysed to 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI), colourless needles (from aqueous methanol), m. p. 144° (Found : C, 68·8; H, 5·3; N, 9·7. Calc. for $C_{17}H_{16}ON_2S$: C, 68·9; H, 5·4; N, 9·5%).

4-2′-Hydroxyethylimino-1-methyl-5 : 5-pentamethylene-2-thiohydantoin was obtained in 55% yield by heating 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) with aqueous 2-aminoethanol. The oily product solidified on cooling and trituration with ether, and crystallised from methanol–ether in colourless prisms, melting incompletely at 158—159° and clearing at 174—175° (Found, on material dried *in vacuo* at 56° : N, 15·5; on material dried *in vacuo* at 140° for 4 hours : N, 17·8. $C_{11}H_{19}ON_3S,2H_2O$ requires N, 15·2%; $C_{11}H_{19}ON_3S$ requires N, 17·4%). The same compound was obtained in quantitative yield by heating 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII) (1·15 g.) with 2-aminoethanol (0·6 g.) at 110—120° for 15 minutes. Hydrolysis of this compound with boiling 20% hydrochloric acid gave, in 91% yield, 1-methyl-5 : 5-pentamethylene-2-thiohydantoin (VIII), colourless needles (from aqueous methanol), m. p. 153° (cf. D). 4-2′-Hydroxyethylimino-5 : 5-pentamethylene-2-thiohydantoin, m. p. 245°, 4-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 255° (decomp.), and 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°, were prepared by the action of 2-aminoethanol on the corresponding methylthio-derivatives, and were identical with the products described in Part II. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI), with 2-aminoethanol at 110—120° for 10 minutes, gave *2-2′-hydroxyethylimino-5 : 5-pentamethylene-4-thiohydantoin*, colourless prisms (from methanol), m. p. 193—194° (Found : C, 52·8; H, 7·3; N, 18·3. $C_{10}H_{17}ON_3S$ requires C, 52·9; H, 7·5; N, 18·5%). This compound, on treatment with methyl iodide and methanolic sodium hydroxide as described in A, gave an oil (91%), which was not analysed but apparently consisted in the main of 4-methylthio-2-2′-hydroxyethylimino-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline, since on acid hydrolysis it lost methanethiol and gave 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°, identical with that described above and in Part II. The oily methylthio-derivative was heated with 2-aminoethanol at 130—140° for ½ hour. Methanethiol was evolved and the product was a water-soluble glass, which crystallised from methanol–ether to give *2 : 4-di-(2′-hydroxyethylimino)-5 : 5-pentamethylenehydantoin*, small colourless prisms, m. p. 117—118° (Found : N, 21·5. $C_{12}H_{22}O_2N_4$ requires N, 22·0%). This product, too, was hydrolysed by acid to 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°.

(G) *Miscellaneous.—a-Methylaminodiphenylacetamide.* a-Chlorodiphenylacetamide (5 g.) (Steinkopf, *loc. cit.*) was heated in a sealed tube at 80—90° for 20 hours with a saturated solution of methylamine in benzene (50 c.c.). The contents of the tube were filtered from methylamine hydrochloride, evaporated to dryness, and recrystallised from methanol to give *a-methylaminodiphenylacetamide*, m. p. 191° (2·7 g., 55%) (Found : N, 11·3. $C_{15}H_{16}ON_2$ requires N, 11·65%). This was recovered unchanged after being heated with carbon disulphide in ethanol in a sealed tube at 80—90° for 20 hours.

5 : 5-Diphenyl-3-benzylhydantoin.—To a solution of 5 : 5-diphenylhydantoin (6 g.) in ethanol (50 c.c.) were added benzyl chloride (3 g.) and a solution of sodium hydroxide in the minimum of water. The mixture was heated under reflux for 17 hours and was poured into water. The solid product was filtered off and recrystallised from methanol to give *5 : 5-diphenyl-3-benzylhydantoin*, m. p. 151° (5·7 g., 70%) (Found : N, 7·9. $C_{22}H_{18}O_2N_2$ requires N, 8·2%).

5 : 5-Diphenyl-3-benzyl-1-methylhydantoin.—To a solution of 5 : 5-diphenyl-3-benzylhydantoin (3·4 g.) in ethanol (50 c.c.) were added 20% aqueous sodium hydroxide (2 c.c.) and methyl sulphate (1·3 g.). The mixture was heated under reflux for 4 hours, cooled, and filtered. The filtrate was poured into water, and the oil which separated crystallised on storage. Recrystallisation from methanol gave *5 : 5-diphenyl-3-benzyl-1-methylhydantoin*, m. p. 125° (1·5 g., 42%) (Found : N, 8·1. $C_{23}H_{20}O_2N_2$ requires N, 7·9%). Attempts to debenzylate this compound by hydrogenation in methanol solution using a palladium–charcoal catalyst at 100° were unsuccessful; the starting material was recovered unchanged.

1-Methyl-5 : 5-pentamethylenehydantoin.—a-Methylaminohexahydrobenzonitrile (42 g.) was suspended in water (100 c.c.) and neutralised by the addition of 36% hydrochloric acid. A solution of potassium cyanate (27 g. in 50 c.c. water) was added at 30—35° with stirring, and the mixture was stirred for a further ½ hour. The *ureide* separated as an oil which crystallised, and was filtered off. A sample, recrystallised from methanol in colourless needles, had m. p. 167—168° (Found : C, 59·9; H, 8·0; N, 23·0. $C_9H_{15}ON_3$ requires C, 59·7; H, 8·3; N, 23·2%). It was suspended in water (100 c.c.) with stirring, and 36% hydrochloric acid (40 c.c.) was added. The solid went into solution and the product separated. The mixture was heated to 80—90° on the steam-bath for 15 minutes to complete the reaction, and then cooled, and the *product* (II) filtered off, washed with cold water, and recrystallised from hot water as long needles, m. p. 174° (20 g., 36%) (Found : C, 59·5; H, 7·6; N, 15·0. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

5 : 5-Pentamethylene-2 : 4-dithiohydantoin.—The light absorption of this compound (XII) showed maxima at 2270 and 2970 A., and $\varepsilon = 5,540$ and 26,300 respectively.

The authors express their thanks to Dr. F. R. Cropper for the light-absorption measurements, and to Mr. G. Bratt and Miss M. Smith for invaluable technical assistance. Microanalyses were carried out by Messrs. Weiler and Strauss, Oxford.

IMPERIAL CHEMICAL INDUSTRIES LTD.,
RESEARCH LABORATORIES, HEXAGON HOUSE,
MANCHESTER, 9.

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80. *Hydroaromatic Steroid Hormones. Part I. 10-Nortestosterone.*

By Arthur J. Birch.

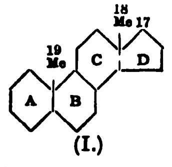
The problem of making physiologically active hormone substitutes is discussed, and the preparation of 10-nortestosterone (IV) is described.

One of the chief difficulties associated with the synthesis of steroid hormones is the quaternary nature of the carbon atoms which carry the angular methyl groups. This difficulty has contributed to prevent the synthesis of the non-aromatic hormones containing two such groups, and there is no known method of introducing the 19-Me (cf. I) into the synthetic aromatic hormones such as (+)-œstrone (ring A aromatic) to produce hydroaromatic compounds convertible into non-aromatic hormones such as testosterone. The only successful attempt on a model substance is that of Woodward (*J. Amer. Chem. Soc.*, 1940, **62**, 1208), but the reaction apparently failed with œstrone.

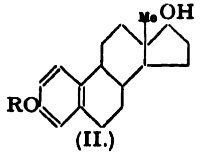
With the increasing importance of steroid hormones, it seems necessary to examine more closely the structural requirements for physiological activity, in particular whether this is retained by compounds lacking the angular methyl groups and therefore available by the reduction of aromatic systems. Œstrogenic activity is comparatively unspecific and is shown by compounds differing greatly in structure from the natural hormones, but for the androgenic, progestational, and cortical hormones even slight changes in the space-distribution of groups are sufficient to depress or abolish activity. Evidence is, however, available in several cases that the 19-Me (between rings A and B) is not absolutely essential for activity. Dirscherl, Kraus, and Voss (*Z. physiol. Chem.*, 1936, **241**, 1; cf. Schering-Kahlbaum A.-G., B.P. 423,287/1935) reported the reduction of (+)-œstrone to an octahydro-derivative (ring A fully reduced and hydroxyl in the 17-position) which is androgenic, and must be considered as the first synthetic compound with this activity; and Ehrenstein (*J. Org. Chem.*, 1944, **9**, 435) obtained a 19-norprogesterone which is claimed to be as active as progesterone itself. He also prepared a 19-nordeoxycorticosterone, which is, however, inactive. Neither of these last two products could be crystallised and they are probably mixtures of isomers.

The 18-Me (between rings C and D) appears to be essential for high activity, at least with the œstrogenic hormones equilenin and œstrone, but this effect may be due merely to the fact that it prevents the (natural) *trans*-junction of rings C and D from assuming the more stable *cis*-configuration. The methyl group can be replaced by ethyl or *n*-propyl without great diminution in activity (Bachmann and Holmes, *J. Amer. Chem. Soc.*, 1940, **62**, 2750). With two fused six-membered rings, the *trans*-junction is the more stable, and it is known that if ring D of the natural hormones is converted into a six-membered ring the compounds obtained are highly active (Goldberg and Wyndler, *Helv. Chim. Acta*, 1943, **26**, 1142; Goldberg and Studer, *ibid.*, 1941, **24**, 478), so it may be possible to omit the 18-Me in such cases.

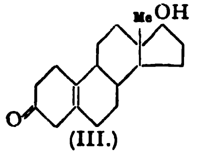
The synthetic approach to nor-steroid hormones has now been greatly simplified by Birch and Mukherji's method of reduction (*Nature*, 1949, **163**, 766; *J.*, 1949, 2351), by which an aryl glyceryl or an aryl 2-hydroxyethyl ether is reduced with sodium and an alcohol in liquid ammonia, and the dihydro-derivative so obtained hydrolysed to an unsaturated ketone. "α"-Œstradiol 1′-glycerol ether [II; R = $CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OH$] was thus reduced to (III), the constitution of which has now been further confirmed by its lack of a light-absorption maximum in the region 2200—3000 A. This βγ-unsaturated ketone has now been isomerised by ethanolic sodium ethoxide to the αβ-unsaturated ketone (IV), which is a 10-*nortestosterone*. Although two stereoisomers are to be expected from the isomerisation, only one crystalline product (orientation at $C_{(10)}$–H unknown) could be isolated (in 60% yield), the remainder being a gum. The constitution assigned to the compound is confirmed by its light absorption in ethanol, with a maximum at 2400—2415 A., $\epsilon_{max.}$ 17,000, and a low-intensity band at 3075 A., $\epsilon_{max.}$ 92·5. Dannenberg (*Abhandl. preuss. Akad. Wiss.*, 1939, **21**, 3) gives for testosterone in ethanol a band at 2410 A., log $\epsilon_{max.}$ 4·20.



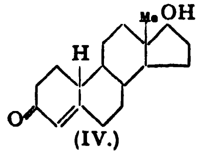
(I.)



(II.)



(III.)



(IV.)

The advantages of the reduction method are that ring A can be kept aromatic up to the last stages, thus simplifying synthetic reactions on the other parts of the molecule; and that a *cyclo*hexenone ring is produced which is characteristic of hormones such as testosterone, progesterone, cortisone, and corticosterone. It is possible in many cases to protect groups such as carbonyl during the reduction (Birch, unpublished work).

This work is being pursued with the object of making further hormone analogues from (+)-œstrone in order to see whether the expenditure of effort necessary for the complete synthesis of such nor-steroids is likely to be justified.

EXPERIMENTAL.

10-*Nortestosterone* (IV).—The following method is somewhat better than that already given (Birch and Mukherji, *loc. cit.*) for the preparation of (III). "α"-Œstradiol 1′-glycerol ether (980 mg.) was dissolved in warm ethanol (30 c.c.) and stirred into liquid ammonia (300 c.c.). Potassium (3 g.) was rapidly added in small pieces with stirring and, after the reaction was complete, water (75 c.c.) was used to decompose the mixture. The ammonia was rapidly evaporated, finally under reduced pressure, and the solution just neutralised by the addition of hydrochloric acid, followed by sufficient acid to give a 5%-acid solution. This solution, containing a suspension, was then shaken with ethyl acetate (30 c.c.), which eventually dissolved the gummy solid as hydrolysis proceeded. The ethyl acetate solution was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was taken up in ethyl acetate (5 c.c.) and chromatographed on alumina (cf. Birch and Mukherji, *loc. cit.*) in the same solvent. The eluate was divided arbitrarily into fractions until evaporation under reduced pressure gave a non-crystallisable gum instead of a solid. The collected solid recrystallised from ethyl acetate as large flat prisms (215 mg.), m. p. 187—188°, $\lambda_{\text{infl.}}$ 2720—2940 A., $\varepsilon_{\text{infl.}}$ 51·4 (ethanol). This compound (III) (200 mg.) was dissolved in warm ethanol (10 c.c.) and added to a solution of sodium (15 mg.) in ethanol (4 c.c.). The mixture was kept at 50° for 5 minutes under nitrogen. After acidification with a few drops of acetic acid the solvent was removed under reduced pressure, and the residue washed with water, taken up in ethyl acetate (5 c.c.), and chromatographed on alumina (cf. Birch and Mukherji, *loc. cit.*) in the same solvent. The first fractions crystallised on removal of the solvent, and 10-*nortestosterone* (IV) was crystallised from light petroleum (b. p. 60—80°) containing a few drops of ethyl acetate, as large colourless prisms (120 mg.), m. p. 111°; $\lambda_{\text{max.}}$ 2400—2415 A., $\varepsilon_{\text{max.}}$ 17,000; $\lambda_{\text{max.}}$ 3075 A., $\varepsilon_{\text{max.}}$ 92·5 (ethanol) (Found: C, 78·5; H, 9·3. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%).

This work was carried out during the tenure of the Smithson Research Fellowship of the Royal Society. The author is grateful to Professor Sir Robert Robinson, P.R.S., for a gift of (+)-œstrone, to Professor A. R. Todd, F.R.S., for the hospitality of his laboratory, and to Dr. R. N. Haszeldine for the absorption spectra.

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 25th,* 1949.]

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81. *Decomposition of Chromic Acid in Sulphuric Acid. The First-order Thermal Reaction.*

By ERNEST E. AYNSLEY.

The thermal decomposition of chromic acid in sulphuric acid between 140° and 170° has been studied. In concentrated solution the reaction is complex, but in 81·5% sulphuric acid and with concentrations of solute <0·05N. a reaction of first order with respect to chromic acid occurs with an activation energy of 10·3 ± 0·5 kcals. At high acid concentrations chromic sulphate inhibits the decomposition, but its effect decreases as the sulphuric acid concentration falls and disappears in about 82% sulphuric acid. In more dilute acid chromic sulphate slightly catalyses the decomposition of chromic acid. The effect of stirring on the reaction has been examined.

THE stability of chromic acid in hot sulphuric acid is of interest because these solutions are used in the determination of such oxidisable vapours as ether (*e.g.*, Schaffer and Ronzoni, *J. Biol. Chem., Baltimore*, 1923, **57**, 741). Snethlage's work (*Rec. Trav. chim.*, 1936, **55**, 712, 874) with unstirred (*vide infra*) sulphuric acid at 138°, and fuming acid at 100°, was believed to show that two reactions occur (in the main simultaneously): (i) a reaction of first order with respect to chromic acid, with a velocity coefficient rising with increasing sulphuric acid concentration up to 99% and thereafter much more rapidly, and (ii) a reaction of second order with respect to chromic acid, with a velocity coefficient rising with the sulphuric acid content up to a concentration of 81% and then falling as the concentration rose to 99%. Chromic sulphate, prepared by reducing chromic acid in sulphuric acid with mannitol or salicylic acid, was found to catalyse the decomposition of chromic acid, the effect decreasing as the concentration of the sulphuric acid was increased and becoming negative in sulphuric acid stronger than 95%.

The speed of decomposition at 138°, even in the most favourable concentrations of acid is not high. Snethlage followed the quickest reaction only to 50% and the slower reactions to less than about 15%. In the present work, with 0·010—0·702N-chromic acid, higher temperatures (140—170°) were employed, thus enabling the reaction to be followed nearly to completion.

EXPERIMENTAL.

Solutions were prepared by shaking the solid with sulphuric acid, setting the mixtures aside for 24 hours, and filtering them through sintered glass. 25-Ml. portions were heated in a 100-ml., Hysil, round-bottomed flask closed with a hollow stopper carrying a 6″ glass stem through which passed a glass stirrer. Precaution was taken to prevent access of dust or other contaminants, and it was shown that there was no appreciable change in the moisture content during the heating which was by a large bath of liquid paraffin maintained within ±0·2° of the desired temperature. For a determination the flask was cooled in boiling water, followed by cold water, and its contents washed into excess of water and titrated with standard ferrous and permanganate solutions.

Table I establishes that equivalent solutions of potassium dichromate, ammonium dichromate, and chromic acid in sulphuric acid behave identically, presumably as a complex involving chromic acid, and since pure potassium dichromate is readily available it was used throughout. Potassium sulphate is without measurable influence: an excess of 50 molecular parts increased the hourly decomposition of 0·06N-potassium dichromate in 99·05% sulphuric acid by only 1·6%.

TABLE I.

Percentage losses in one hour in 99·15% H_2SO_4 *at* 160°.

Normality of solution.	$K_2Cr_2O_7$.	$(NH_4)_2Cr_2O_7$.	CrO_3.
0·010	18·0	17·8	17·9
0·025	17·7	17·9	18·1
0·100	17·9	18·0	18·3
0·150	17·5	18·2	18·5
0·250	18·0	18·5	18·8
0·400	18·6	18·9	19·1

An effect on the course of the reaction which has not previously been observed is that of stirring. In solutions of lower concentrations the rate of decomposition may be increased as much as 27% by this means, but in concentrated solutions (about 0·7N.) the rates in stirred and in unstirred solutions are identical. Both conditions yielded reproducible results. Since precautions were always taken to see that a solution was at the required temperature before timing a run, the difference cannot be a result of the unstirred mixtures not being at the temperatures of the paraffin bath, the low thermal conductivity, or the lack of convection in the system. The acceleration is not affected by oxygen because, when the solution is agitated by a stream of preheated oxygen, admittedly less effectively than by the stirrer, a 20·1% increase was recorded in a 0·15N-solution of potassium dichromate in 99% sulphuric acid. This suggests that the reaction is not reversed by molecular oxygen. Nor was it due to increased contact with the surface since a 20-fold increase in the glass surface was without influence on the reaction, which is presumed homogeneous. Snethlage used unstirred solutions; the results reported in this work were obtained in stirred solutions.

FIG. 1.

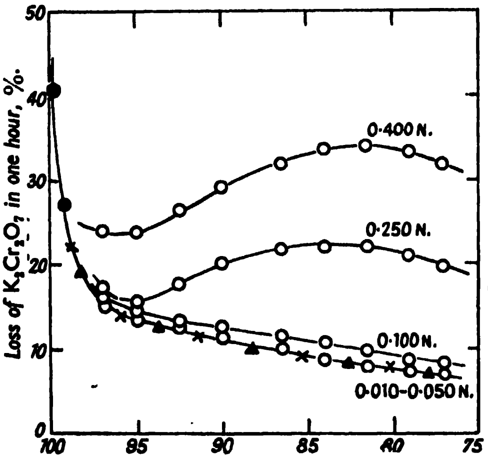
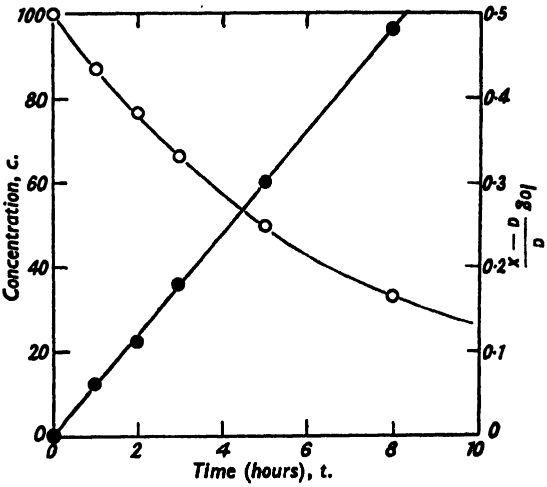


FIG. 2.



0·05N-CrO_3 *in* 81·5% H_2SO_4 *at* 170°.

Figure 1 shows the initial percentage losses, per hour, of chromic acid in sulphuric acid of different strengths at 160°, for six concentrations of solute. Clearly in more concentrated solutions of chromic acid the reaction is complex and reaches a maximum speed in 81·5% sulphuric acid. At a solute concentration of <0·1N., the initial speed falls steadily with decreasing sulphuric acid concentration and at concentrations less than 0·05N. the initial percentage losses per hour are almost identical in all acid concentrations. In acid solutions stronger than 99% there is a rapid increase in speed and the initial percentage losses are identical for all concentrations of solute. However, in fuming acid the decomposition is so rapid that accurate measurement is difficult.

Table II shows that in 99·15% sulphuric acid at 160° there is a fall in the reaction rate as the heating proceeds, shown by the decreasing values of k calculated from the first-order equation $k = (2{\cdot}303/t) \log_{10} 100/(100 - x)$ (t = time of heating in seconds, and x = the percentage loss of chromic acid in time t).

TABLE II.

Heating periods (160°) in hours. Values of $k \times 10^5$. 99·15% H_2SO_4.

Normality.	1 hr.	2 hr.	4 hr.	8 hr.	16 hr.	Normality.	1 hr.	2 hr.	4 hr.	8 hr.	16 hr.
0·025	5·41	4·96	3·95	3·51	2·98	0·150	5·28	4·53	3·63	3·15	2·84
0·050	5·51	4·80	3·78	3·46	—	0·400	5·72	4·86	4·17	3·47	—
0·075	5·44	4·70	3·72	3·23	—	0·702	6·24	5·67	4·86	4·32	—
0·100	5·48	4·45	3·56	3·13	—						

This fall in speed is due to chromic sulphate which is a by-product of the reaction, and comparable results can be obtained by using added chromic sulphate. Table III gives (*a*) the percentage losses observed in the first hour at 160° in a 0·025N-chromic acid solution in 99·15% sulphuric acid to which different amounts of chromic sulphate (prepared by reducing chromic—sulphuric acid solutions with sulphur dioxide) were added and, for comparison, (*b*) the calculated percentage losses in solutions containing the decomposition product $Cr_2(SO_4)_3$ equal in concentration to that added in (*a*).

TABLE III.

r = ratio $Cr_2(SO_4)_3/CrO_3$. 0·025N-CrO_3 in 99·15% H_2SO_4 at 160°.

$r = 0$.	$r = 0{\cdot}5$.		$r = 0{\cdot}6$.		$r = 0{\cdot}8$.		$r = 1{\cdot}0$.		$r = 2{\cdot}3$.	
	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)
17·7	13·9	13·0	12·6	12·0	9·7	9·4	9·3	9·2	9·1	9·0

The results indicate that the poisoning effect is due to chromic sulphate and that there is a concentration limit to this effect, *viz.*, $1Cr_2(SO_4)_3 : 1CrO_3$. The poisoning effect falls as the sulphuric acid concentration falls and it disappears in about 82% acid. Below this acid concentration, chromic sulphate has a slight catalytic effect. Thus, at 160° in a 0·06N-CrO_3–80% H_2SO_4 solution with $r = 4$, a 10% increase in the decomposition in one hour was observed.

Working with 81·5% acid and using concentrations of solute <0·05N. it was shown that within these narrow limits the reaction obeys reasonably well a kinetic equation of the first order with respect to dichromate, as is shown by (i) the constant values of k at all temperatures (Table IV), (ii) Fig. 2 which shows a typical set of these results plotted as (*a*) concentration against time and (*b*) log $[a/(a - x)]$ against time, and (iii) Table V which gives the times of one-fifth conversion for the same set of results.

TABLE IV.

Values of k × 10^5 *in* 81·5% H_2SO_4.

		Heating periods in hours.				
Temp.	Normality of solution.	1.	2.	3.	5.	8.
170°	0·050	3·9	3·6	3·8	3·9	3·9
	0·025	3·8	3·7	3·7	3·6	3·7
	0·010	3·7	4·0	3·6	3·5	3·8
165	0·050	2·9	2·8	2·9	2·8	2·6
	0·025	2·8	2·8	3·0	2·9	2·7
	0·010	3·0	2·9	3·0	2·7	2·7
160	0·050	2·1	2·2	2·2	2·1	2·0
	0·025	2·3	2·3	2·3	2·0	2·1
	0·010	2·2	2·2	2·1	2·2	2·0
155	0·050	1·6	1·7	1·6	1·6	1·5
	0·025	1·7	1·6	1·5	1·7	1·6
	0·010	1·6	1·6	1·5	1·6	1·5
150	0·050	1·2	1·2	1·2	1·0	1·1
	0·025	1·1	1·3	1·2	1·3	1·2
	0·010	1·0	1·1	1·3	1·2	1·3

TABLE V.

Concn., %	100	80	60	50	40
$t_{1/5}$ (hours)	1·7	1·6	1·5	1·5	1·7

From these results the plots of $\log_{10} k$ against $1/T$ gives a straight line from which an Arrhenius activation energy of 10·3 ± 0·5 kcals. is obtained.

Analysis of the results shows that the thermal decomposition of chromic acid in sulphuric acid is complex in all solutions (except those within the narrow concentration limits of 81·5% sulphuric acid and solute concentration less than 0·05N. where a reaction of the first order prevails) and cannot be adequately accounted for by assuming a second-order reaction to be superimposed on a first-order reaction. Moreover, chromic sulphate is found to poison the reaction down to 82% sulphuric acid and thereafter to act as a mild catalyst. These results are not in agreement with those of Snethlage who found chromic sulphate to be a poison down to 95% H_2SO_4 and in more dilute sulphuric acid solutions to be a powerful catalyst.

INORGANIC CHEMISTRY LABORATORIES,
KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1.

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82. *Anhydrides of Polyhydric Alcohols. Part XIII. The Amino-derivatives of* 1 : 4-3 : 6-*Dianhydro-mannitol, -sorbitol, and* -L-*iditol, and their Behaviour towards Nitrous Acid.*

By V. G. BASHFORD and L. F. WIGGINS.

The behaviour of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-mannitol and -sorbitol towards nitrous acid has been investigated. It has been found that in both cases the only product isolated was 1 : 4-3 : 6-dianhydro-L-iditol, the formation of which must have involved Walden inversion at $C_{(2)}$ and $C_{(5)}$, and $C_{(5)}$, respectively. The similarity between this phenomenon and that occurring when 2 : 4-3 : 5-dimethylene D-gluco- and -D-manno-saccharic acids are epimerised is emphasised. Although the replacement of the toluene-*p*-sulphonyl groups in 2 : 5-ditoluene-*p*-sulphonyl 1 : 4-3 : 6-dianydro-mannitol and -sorbitol proceeds smoothly with the formation of the corresponding diamines, the attempt to prepare the diamine from 1 : 4-3 : 6-dianhydro-L-iditol by the same procedure failed; in this case a secondary amine was formed which on the basis of its physical and chemical properties and, as a result of scale-model studies, is tentatively allocated the structure, 2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 . 5-*dideoxy*-D-*mannitol*. Further work designed to confirm or reject this conjecture is in progress.

IN view of the interesting facts that have come to light during study of the deamination of amino-derivatives of partly substituted sugar derivatives containing hydroxyl groups situated *trans* to the amino-groups (Wiggins, *Nature*, 1946, **157**, 300) it was held worth while to investigate the deamination of the diamino-derivatives of the 1 : 4-3 : 6-dianhydrides of the epimerically related hexitols, D-mannitol, D-sorbitol, and L-iditol in which no free hydroxyl groups exist. A preliminary account of this work has already appeared (Bashford and Wiggins, *Nature*, 1949, **164**, 573). The deamination of amino-sugars such as 4 : 6-benzylidene 3-amino-α-methyl-3-deoxyaltroside led to the formation of ethylene oxide anhydro-rings, this particular amine giving 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside. The same phenomenon has been observed not only with appropriate glycoside derivatives, but also with those of 1 : 6-anhydro-sugars and sugar alcohols (Bashford and Wiggins, forthcoming publication).

If 2 : 5-diamino-dianhydro-2 : 5-dideoxyhexitols were deaminated, no such anhydro-ring formation could take place. Deamination of these substances might be expected to occur without Walden inversion, by analogy with the behaviour, towards alkaline reagents, of toluene-*p*-sulphonyl derivatives of sugars which contain no free hydroxyl group, or no hydroxyl group situated *trans* to the toluene-*p*-sulphonyloxy residue. Thus, 3-toluene-*p*-sulphonyl 1 : 2-5 : 6-di*iso*propylidene glucose (I) was hydrolysed by alkaline reagents without Walden inversion, to give di*iso*propylidene glucose (II). This contrasts with behaviour of compounds such as 2-toluene-*p*-sulphonyl 4 : 6-benzylidene α-methylglucoside (III), the alkaline hydrolysis of which is accompanied by Walden inversion: for from (III), 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (IV) is formed.

Deamination of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (V; R = NH_2) and -sorbitol (VI; R = NH_2) might be expected to lead only to the parent hexitols, 1 : 4-3 : 6-dianhydro-mannitol, (V; R = OH) and -sorbitol (VI; R = OH) respectively, especially since deamination of 4 : 6-benzylidene 3-amino-α-methyl-3-deoxyaltroside (VII) follows the same course as alkaline hydrolysis of 2-toluene-*p*-sulphonyl 4 : 6-benzylidene α-methylglucoside and gives rise to 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (IV). When, however, 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol was treated with sodium nitrite in acid solution and the liquid product treated with methanesulphonyl chloride, the dimethanesulphonate, m. p. 156°, of 1 : 4-3 : 6-dianhydro-L-iditol (Wiggins, *J.*, 1948, 1403) was obtained. This product was also isolated after similar treatment of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-

dideoxysorbitol. Although in neither case was any other dianhydrohexitol derivative isolated, the small yield of the L-iditol derivative indicated that it was not the only product. The fact that

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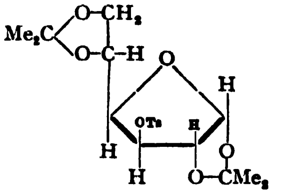

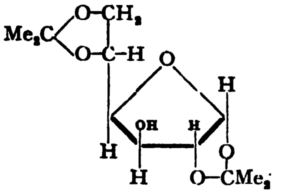

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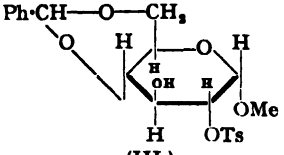

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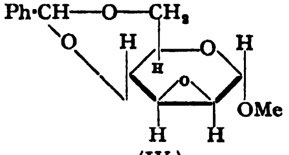

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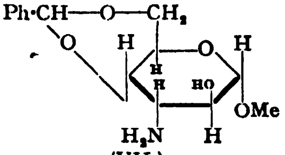

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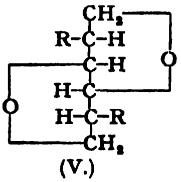

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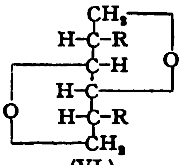

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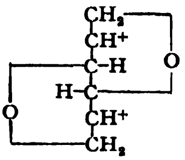


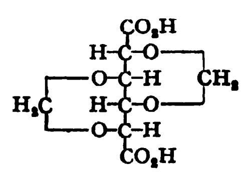
(VIII.)

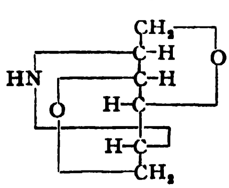
(Ts = toluene-*p*-sulphonyl.)

an L-iditol derivative has been obtained from both diamino-dianhydrodideoxyhexitols means that the deamination has been accompanied by Walden inversion, in the case of sorbitol at $C_{(5)}$, and in that of mannitol at both $C_{(2)}$ and $C_{(5)}$. This is explicable since deamination must involve the transitory formation of the carbonium cation (VIII) and this, on hydroxylation may take up the configuration of D-mannitol, D-sorbitol, or L-iditol. That in fact it takes up that of L-iditol to the apparent exclusion of the other two seems to indicate a configurational stability peculiar to this hexitol. The behaviour of the diamino-dianhydrohexitols towards deamination is in marked contrast to the alkaline hydrolysis of 3-toluene-*p*-sulphonyl di*iso*propylidene glucose, where Walden inversion, although possible because of the likelihood of the transitory formation of a carbonium cation (at $C_{(3)}$), does not take place.

This conversion of dianhydro-mannitol and -sorbitol into the corresponding derivative of L-iditol is paralleled by the epimerisation of 2 : 4-3 : 5-dimethylene D-manno- and D-gluco-saccharic acid. When a solution of the dimethyl ester of either of these acids is boiled with barium hydroxide solution, epimerisation occurs with the formation of 2 : 4-3 : 5-dimethylene L-ido-saccharic acid (IX) (Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61). In this case,

(IX.)

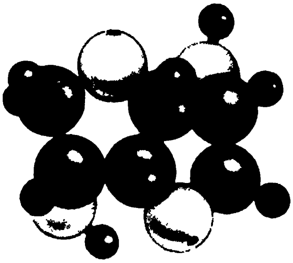




(X.)

however, the ready isolation of dimethylene L-idosaccharic acid may be caused merely by the ease with which this substance crystallises or to its lower solubility In fact the alkaline hydrolysis of dimethyl dimethylene D-glucosaccharate did afford some dimethylene D-gluco-saccharic acid as well as the L-idosaccharic acid derivative. On the other hand, similar treatment of the corresponding mannosaccharic acid derivative gave only (IX).

Another example of the conversion of 1 : 4-3 : 6-dianhydro-mannitol and -sorbitol into dianhydro-L-iditol is given by Fletcher and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 939), who treated each of these derivatives with Raney nickel and then hydrogenated them in the presence of that catalyst. Again dianhydro-L-iditol was the only product isolated in quantity. Lew, Wolfrom, and Goepp (*J. Amer. Chem. Soc.*, 1945, **67**, 1865) however claim to have demonstrated the presence of all three dianhydrides in the reaction product, by chromatographic methods.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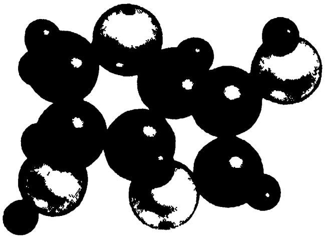
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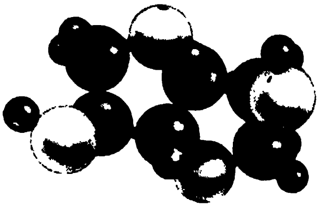
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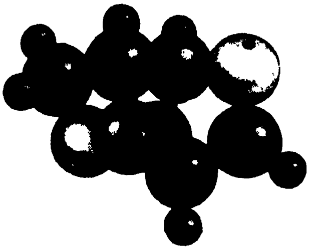
(4)

(1) 1 : 4-3 : 6-*Dianhydro*-D-*mannitol.*
(2) 1 : 4-3 : 6-*Dianhydro*-D-*sorbitol.*
(3) 1 : 4-3 : 6-*Dianhydro*-D-*iditol.*
(4) 2 : 5-*Imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol* (*inverted to show the imine bridge*).

In order to test whether the deamination of 2 : 5-diamino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-L-iditol would lead solely to the formation of dianhydro-L-iditol the attempt was made to prepare this diamine. 1 : 4-3 : 6-Dianhydro-L-iditol was converted into the 2 : *5-di-toluene*-p-*sulphonate* and this treated with methyl-alcoholic ammonia in the manner found successful for the preparation of the diamines of dianhydro-mannitol and -sorbitol (Montgomery and Wiggins, *J.*, 1946, 393). No diamine was obtained however; instead a substance having only one nitrogen atom per six carbon atoms was isolated. This was a base, $C_6H_9O_2N$, which had m. p. 99—100°, $[\alpha]_D$ +90·5°, and formed a crystalline *oxalate, picrate,* and *hydrochloride.* It gave no Schiff base with salicylaldehyde; it lost no nitrogen on treatment with nitrous acid, but afforded a crystalline *N*-nitroso-derivative giving the characteristic Liebermann colour reaction with phenol and sulphuric acid. The compound $C_6H_9O_2N$ is therefore a dianhydro-hexitol containing a secondary amino-group, and the only way in which this can be reconciled with the analytical data of the compound and its derivatives is to assume the formation of an imine bridge between $C_{(2)}$ and $C_{(5)}$. An immediate difficulty arises as scale models show that it is impossible so to join $C_{(2)}$ to $C_{(5)}$ of the 1 : 4-3 : 6-dianhydro-L-iditol. The imino-compound $C_6H_9O_2N$ must therefore possess a different configuration. Since the reaction conditions preclude the likelihood of there being any alteration to the ring structure and hence of the configuration about $C_{(3)}$ and $C_{(4)}$ the only possible configurations are those of D-mannitol and D-sorbitol. Configurational changes about $C_{(2)}$ and $C_{(5)}$ are certainly possible because the removal of toluene-*p*-sulphonyloxy-groups by alkaline reagents must involve the transitory formation of the carbonium cation (VIII). From scale models of the three epimerically related 1 : 4-3 : 6-dianhydrohexitols (shown in the figure) it is clear that the only one in which $C_{(2)}$ and $C_{(5)}$ could be bridged by an imine group is 1 : 4-3 : 6-dianhydro-D-mannitol. Hence it is tentatively suggested that the compound $C_6H_9O_2N$ obtained by the action of ammonia on 2 : 5-di-toluene-*p*-sulphonyl 1 : 4-3 : 6-dianhydro-L-iditol is 2 : *5-imino-*1 : 4-3 : *6-dianhydro-*2 : *5-dideoxy-*D-*mannitol* (X).

EXPERIMENTAL.

Deamination of 2 : *5-Diamino-*1 : 4-3 : *6-dianhydro-*2 : *5-dideoxysorbitol.*—The diamine (3·95 g., prepared according to Montgomery and Wiggins *J.*, 1946, 393) was dissolved in water (25 c.c.) and acidified with dilute hydrochloric acid. Sodium nitrite (4·5 g.) dissolved in water (25 c.c.) was then added and the mixture kept overnight. Thereafter the solution was neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure. The dry residue was extracted exhaustively with hot ethyl acetate, and the extracts were evaporated to a syrup (1·68 g.). This distilled at 115—130° (bath temperature)/0·05 mm. as a light-yellow oil (1·27 g.), $[\alpha]_D$ +46·7° (*c*, 1·9 in acetone).. A portion (0·9 g.) of this distillate was dissolved in dry pyridine (15 c.c.), and methanesulphonyl chloride (1·6 c.c.) added at 0°. After being kept overnight at room temperature, the mixture was poured into water and extracted therefrom with chloroform. The chloroform extract was washed successively with dilute sulphuric acid, sodium hydrogen carbonate solution, and with water, dried ($MgSO_4$), filtered (charcoal), and evaporated to dryness. The residue, crystallised and recrystallised from alcohol, gave needles of 2 : 5-dimethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol, m. p. 156·5° alone or on admixture with authentic material, and had $[\alpha]_D$ +48·0° (*c*, 2·1 in acetone). Further crops of crystals were obtained from the mother-liquors but no other pure substance could be isolated.

Deamination of 2 : *5-Diamino-*1 : 4-3 : *6-dianhydro-*2 : *5-dideoxymannitol.*—The diamine (1·29 g.) (Montgomery and Wiggins, *loc. cit.*) was dissolved in water (30 c.c.), acidified with glacial acetic acid (3 c.c.), and treated with sodium nitrite (1·3 g.). The solution was kept overnight at room temperature and worked up as above. The resultant syrup distilled at 175—180° (bath temperature)/0·001 mm. By repetitions 3·52 g. of the distillate were accumulated. This was treated in dry pyridine (40 c.c.) with methanesulphonyl chloride (9·33 c.c.) at 0°. Thereafter the mixture was kept at room temperature overnight and then poured into water (300 c.c.). A solid (0·76 g.) was deposited and after being recrystallised from methyl alcohol had m. p. 156—157° alone or on admixture with 2 : 5-dimethane-sulphonyl 1 : 4-3 : 6-dianhydro-L-iditol, and $[\alpha]_D$ +48·0° (*c*, 2·1 in acetone). For the isomers of this product see Montgomery and Wiggins (*J.*, 1948, 2204) and Bashford and Wiggins (*J.*, 1948, 299).

2 : *5-Ditoluene-*p-*sulphonyl* 1 : 4-3 : *6-Dianhydro-*L-*iditol.*—To 1 : 4-3 : 6-dianhydro-L-iditol (17·3 g.; Wiggins, *J.*, 1948, 1403) in dry pyridine (75 c.c.) toluene-*p*-sulphonyl chloride (50 g.) was added a little at a time at 0°. The mixture was kept at room temperature for 72 hours and thereafter poured into water. The solid which separated was filtered off, washed, and dried; recrystallised from ethyl alcohol, 2 : *5-ditoluene-*p-*sulphonyl* 1 : 4-3 : *6-dianhydro-*L-*iditol* (44 g.) formed needles, m. p. 90°, $[\alpha]_D$ +38·2° (*c*, 2·0, in chloroform) (Found : C, 52·8; H, 5·1. $C_{20}H_{22}O_8S_2$ requires C, 52·8; H, 4·85%).

Reaction of 2 : *5-Di-toluene-*p-*sulphonyl* 1 : 4-3 : *6-Dianhydro-*L-*iditol with Methyl-alcoholic Ammonia.*—The compound (42 g.) was mixed with dry methyl alcohol (900 c.c.), saturated at 0° with dry ammonia gas, and heated in an autoclave for 30 hours at 160—170°. Thereafter the solution was evaporated to dryness, and the residue heated at 100° with barium hydroxide (50 g.) in water (400 c.c.) (this and all subsequent operations were carried out in an atmosphere of nitrogen). The solution was then evaporated to a syrup under reduced pressure, the water being completely removed by distillation with benzene. The residue was extracted several times with boiling chloroform, and the combined extracts were filtered and evaporated to dryness. The residue, recrystallised from ethyl acetate, formed needles, m. p. 99—100°, $[\alpha]_D$ +90·5° (*c*, 2·56 in chloroform) (2·0 g.). This substance was very volatile and readily sublimed, and it is probable that a large amount of the material was lost during the isolation. It did not form a Schiff base with salicylaldehyde and a trace of alkali. It was 2 : 5-*imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol* [Found : C, 56·4; H, 6·9; N, 10·7%; *M* (Rast), 136·5. $C_6H_9O_2N$ requires C, 56·6; H, 7·1; N, 11·0%; *M*, 127]. The imine (0·05 g.) was dissolved in alcohol (2 c.c.), and picric acid (0·1 g.), also dissolved in alcohol (2 c.c.), was added. Recrystallised from alcohol the *picrate* which separated formed yellow needles (0·11 g.), m. p. 219—220° (decomp.) (Found : N, 16·3. $C_{12}H_{12}O_9N_4$ requires N, 15·8%). The imine (0·07 g.) was dissolved in chloroform (4 c.c.), and the solution saturated with dry hydrogen chloride. After a few seconds a white precipitate separated. The *hydrochloride*, recrystallised from alcohol containing a trace of water, had m. p. 280—290° (decomp.) (Found : C, 44·1; H, 6·0; N, 8·3. $C_6H_9O_2N,HCl$ requires C, 44·3; H, 6·1; N, 8·6%). The imine (0·05 g.) in alcohol (2 c.c.) was treated with an equivalent amount of oxalic acid also dissolved in alcohol. A white solid separated. The mixture was heated to the b. p., and water added drop by drop until complete dissolution was effected. On cooling, the *oxalate* separated; it had m. p. 243° (Found : C, 48·6; H, 5·5. $C_{14}H_{20}O_8N_2$ requires C, 48·8; H, 5·81%).

The mother-liquors after the separation of the imino-compound were concentrated and distilled in two portions : (*a*) b. p. 100° (bath temperature)/0·1 mm. (0·3 g.), and (*b*) b. p. 120—140° (bath temperature)/0·1 mm. (1·52 g.). Fraction (*a*) yielded a further amount of 2 : 5-imino-1 : 4-3 : 6-dianhydro-2 : 5-dideoxy-D-mannitol, but fraction (*b*) was a liquid which has not been identified.

N-*Nitroso-derivative of* 2 : 5-*Imino*-1 : 4-3 : 6-*dianhydro*-2 : 5-*dideoxy*-D-*mannitol*.—The imine (0·5 g.) was dissolved in water, acidified with acetic acid, and treated with sodium nitrite (0·5 g.) dissolved in water, and the mixture kept at room temperature overnight. No evolution of nitrogen was apparent. The solution was neutralised with sodium hydrogen carbonate and evaporated to dryness, and the dry residue exhaustively extracted with hot ethyl acetate. The combined extracts on being evaporated afforded a solid which, recrystallised from ethyl acetate, furnished the N-*nitroso*-derivative, m. p. 121·5°, $[\alpha]_D$ —323° (*c*, 2·43 in chloroform), which gave the characteristic Liebermann test for *N*-nitroso-compounds (Found : C, 45·6; H, 5·1. $C_6H_8O_3N_2$ requires C, 46·2; H, 5·1%).

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THE A.E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15.

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83. *Photochemical Reactions. Part XV.* (a) *Photopolymerisation of Coumarins and Related Substances.* (b) *Photo-addition and -reduction Processes of Aromatic Ketones.*

By ALEXANDER SCHÖNBERG, NAZIH LATIF, RADWAN MOUBASHER, and (in part)
WILLIAM IBRAHIM AWAD.

(*a*) 3-Phenylcoumarin forms a photodimer analogous to that from coumarin; the constitution of the latter dimer is therefore (I*a*) and not (II). Photodimers of 3-phenyl*iso*coumarin and benzylidenephthalide were obtained (cf. IV and III). These dimers gave the monomers when heated.

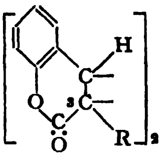
(*b*) From 2 : 7-dimethylphenanthraquinone with stilbene and from phenanthraquinone with 1 : 2-di-4′-pyridylethylene, 3 : 4-diphenyl- and 3-phenyl-*iso*coumarin and 1 : 3-diphenyl*iso*chromen, the photo-products (V), (VI), (VIII), (VII), and (IX) respectively were obtained.

o-Dibenzoylbenzene in *iso*propyl alcohol yielded a photoproduct which, when heated, gave 1 : 3-diphenyl*iso*benzofuran (XI). Phenanthraquinone monoxime and monoimine on photoreduction yielded diphenanthro-oxazine (XIII); with aromatic aldehydes in the presence of light the oxime yielded products which gave 2-arylphenanthro-oxazoles (X) on heating.

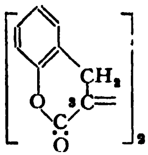
In connection with the constitution of the photoreduction product of triketoindane (XIV) the constitution of a substance erroneously described (Gabriel and Leupold, *Ber.*, 1898, **31**, 1159) as (XVII) is proved to be (XXI).

Photopolymerisations.—(a) *Coumarins*. Formulæ (I*a*) and (II) have been discussed for the product obtained when a solution of coumarin in alcohol or a suspension of the solid in water is exposed to sunlight (Ciamician and Silber, *Ber.*, 1902, **35**, 4130; 1903, **36**, 4266; De Jong, *Rec. Trav. chim.*, 1924, **43**, 318). Formula (II) is still widely used (cf. Richter and Anschütz, " Chemie der Kohlenstoffverbindungen," Vol. II, 2nd half, p. 515, 12th edn., 1935). Fischer has given to the photodimer of umbelliferone methyl ether a formula analogous to (II) (*Arch. Pharm.*, 1941, **279**, 306), but its correctness was questioned by Wessely and Flaichinger (*Ber.*, 1942, **75**, 971).

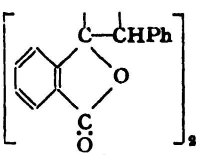
Photodimerisation of coumarin and its derivatives with the formation of (II) or its analogues is possible only when the hydrogen in the position 3 is unsubstituted. We found, however, that 3-phenylcoumarin in sunlight is easily converted in excellent yield into a similar *photodimer*; therefore, the dimers must be *cyclo*butane derivatives (I), a conception which is favoured by regeneration of the monomer when the photodimer of coumarin or of 3-phenylcoumarin is heated.



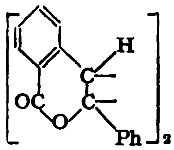
(I; *a*, R = H; *b*, R = Ph.)



(II.)

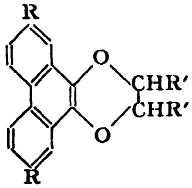


(III.)

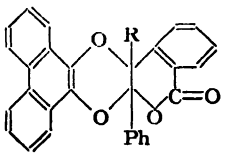


(IV.)

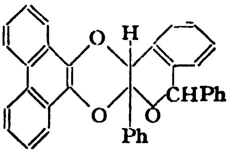
(b) *Benzylidenephthalide and* 3-*phenyl*iso*coumarin.* Both these substances form *photodimers* (III and IV, respectively) under the action of sunlight; when heated, the products regenerate the monomers.



(V; R = Me, R′ = Ph.)
(VI; R = H, R′ = C_5H_4N.)



(VII; R = H.)
(VIII; R = Ph.)

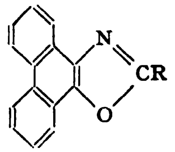


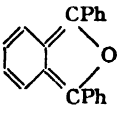
(IX.)

Photoaddition Reactions.—We have continued the investigations on the action of phenanthraquinone on ethylenes (Schönberg, Mustafa, and their co-workers, *J.*, 1944, 387; 1945, 551; 1948, 2126) and have studied the action of 2 : 7-dimethylphenanthraquinone on stilbene and of phenanthraquinone on 1 : 2-di-4′-pyridylethylene, 3 : 4-diphenyl- and 3-phenyl-*iso*coumarin, and 1 : 3-diphenyl*iso*chromen. In all cases colourless or almost colourless addition *products* (V)—(IX) were obtained, some of which, *e.g.*, (VII) and (VIII), regenerated the starting materials when heated.

Phenanthraquinone Monoxime and Aromatic Aldehydes.—The oxime and benzaldehyde do not react in benzene in the dark; in sunlight, however, a product was formed which on heating yielded 2-phenylphenanthro-oxazole (X; R = Ph); in the case of anisaldehyde 2-p-*methoxyphenylphenanthro-oxazole* (X; R = C_6H_4·OMe-*p*) was obtained. These reactions are similar to the photo-formation of 2-arylphenanthro-oxazoles by the action of aromatic aldehydes on phenanthraquinoneimine (Schönberg and Awad, *J.*, 1945, 197).

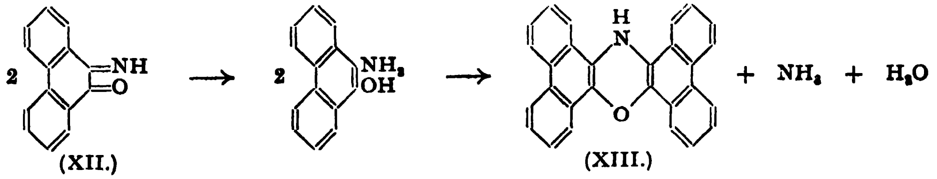
(X.)





(XI.)

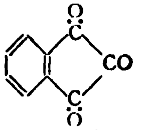
Photoreductions.—Very little is known about the photoreduction of *o*-diketones, *o*-quinone oximes or imines. When *o*-dibenzoylbenzene was exposed to sunlight in *iso*propyl alcohol, a yellow crystalline product was obtained which, when heated, gave 1 : 3-diphenyl*iso*benzofuran (XI) in good yield. Phenanthraquinone monoxime or imine (XII) in *iso*propyl alcohol in sunlight gave diphenanthro-oxazine (XIII) in good yield, probably by way of 10-aminophenanthr-9-ol.

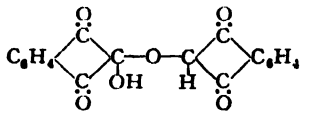


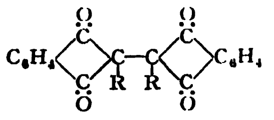
(XII.) (XIII.)

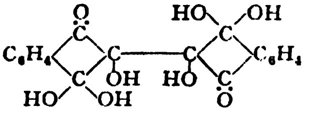
Previously it was shown (Schönberg and Moubasher, *J.*, 1944, 366) that when triketoindane (XIV) in *iso*propyl alcohol was exposed to sunlight and the reaction product crystallised from a mixture containing water, a compound known as hydrindantin was formed, which previously had been obtained by Ruhemann (*J.*, 1911, 99, 797) by reduction of ninhydrin (the hydrate of

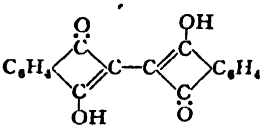
XIV) in the absence of light. Ruhemann believed that hydrindantin was (XV + $2H_2O$), but recently Schönberg and Moubasher (*J.*, 1949, 212) showed that the reactions of this compound do not accord with (XV + $2H_2O$), but do accord with (XVIII). However, there was one obstacle to the new formula : Gabriel and Leupold (*loc. cit.*) described a deep-yellow compound obtained


(XIV.)


(XV.)


(XVI; R = H.)
(XVII; R = OH.)

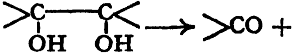

(XVIII.)


(XIX.)

by the action of alkaline hydrogen peroxide on the violet bisindane-1 : 3-dionyl. This yellow compound for which Gabriel and Leupold advanced formula (XVII) cannot be transformed into hydrindantin by the action of water. For the violet compound Gabriel and Leupold erroneously advanced formula (XVI); it has in reality formula (XIX) (cf. Schönberg and Moubasher, *J.*, 1944. 366).

Gabriel and Leupold's oxidation scheme (XVI) ⟶ (XVII) has to be replaced by (XIX) ⟶ (XX) ⟶ (XXI). Formula (XXI) but not (XVII) is in agreement with the deep-yellow colour of the compound and its solubility in sodium hydrogen carbonate solution with evolution of carbon dioxide and its vigorous reaction with diazomethane. *o*-(1 : 3-Diketoindanyl-2-glyoxyloyl)benzoic acid (XXI) on pyrolysis yields indane-1 : 3-dione-2-*spiro*-2′-(1′ : 3′ : 4′-triketo-1′ : 2′ : 3′ : 4′-tetrahydronaphthalene) (XXII) (cf. Radulescu, *Zentr.*, 1923, III, 1081).

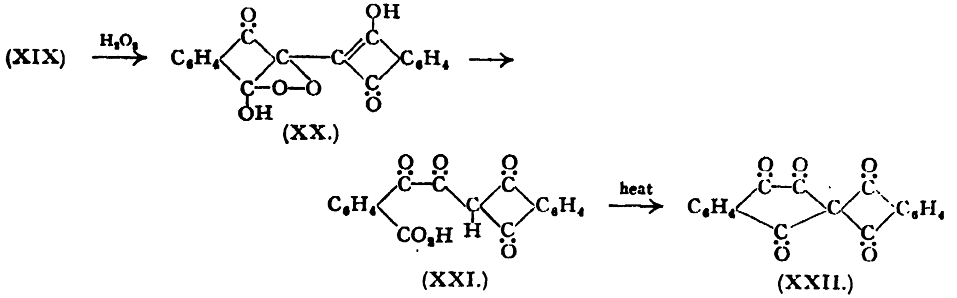
If formula (XVI) were correct, then, on heating, (XVII) should decompose according to the scheme :



$>\underset{OH}{C}-\underset{OH}{C}< \longrightarrow >CO + H_2C<$

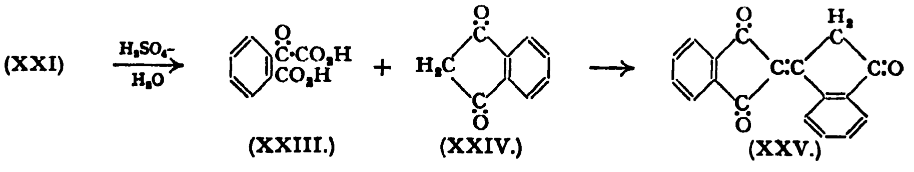
(cf. Schönberg and Mustafa, *J.*, 1944, 305).

Formula (XXI) explains readily the nature of the product actually obtained by pyrolysis, namely (XXII). The hypothetical change (XVII) ⟶ (XXII) can take place only in consequence of a pinacolin rearrangement; however, such rearrangement is not effected by pyrolysis alone, but by heating the pinacols with acids, etc.



(XX.)
(XXI.)
(XXII.)

Acid hydrolysis of (XXI) yields phthalonic acid (XXIII) and 2-(3-ketoindan-1-ylidene)-indane-1 : 3-dione (XXV), which is believed to be formed from the primary product (indane-1 : 3-dione) (XXIV) by autocondensation (cf. Wislicenus and Kötzle, *Annalen*, 1889, 252, 79).



(XXIII.) (XXIV.) (XXV.)

EXPERIMENTAL.

The photochemical reactions were carried out in Pyrex glass tubes, the air having been displaced by dry carbon dioxide and the tube sealed. "AnalaR" benzene which had been dried over sodium was used.

Photopolymerisations.—Coumarin (cf. Ciamician and Silber, *Ber.*, 1914, **47**, 642). Powdered coumarin (3 g.), suspended in water (100 c.c.) in a stoppered 1-l. flask, was exposed to sunlight during October. The solid was filtered off, dried, and extracted several times with ether in which the photodimer was slightly soluble. The dimer recrystallised from glacial acetic acid in almost colourless crystals, m. p. *ca.* 260° (decomp.) (*ca.* 10% yield).

The photodimer was heated under water-pump vacuum at 290° (bath) in a Pyrex test-tube for 1 hour. Oily drops of coumarin (m. p. and mixed m. p.) which accumulated on the upper parts of the reaction vessel solidified after being allowed to cool in a vacuum.

3-Phenylcoumarin. 3-Phenylcoumarin (1 g.) (Meerwein *et al.*, *J. pr. Chem.*, 1939, **152**, 253) in benzene (25 c.c.) was exposed to sunlight during October. Crystals separated gradually, were filtered off, and were washed with ether. A further quantity of the crude photodimer was obtained on concentration of the benzene filtrate, addition of a few drops of ether, and cooling. The crude product was dissolved in the least amount of hot benzene, filtered hot, and left to cool slowly; to the still warm solution, a few drops of ether were added. The *photodimer* (I*b*) slowly separated in colourless crystals, m. p. *ca.* 242° (*ca.* 90%) (Found : C, 81·1; H, 4·7. $C_{30}H_{20}O_4$ requires C, 81·1; H, 4·5%).

Thermal decomposition was carried out as above by heating the material for 1 hour in a boiling ethyl phthalate bath. The oily droplets of 3-phenylcoumarin (m. p. and mixed m. p.) which accumulated at the upper parts of the reaction vessel solidified on cooling in a vacuum and were recrystallised from ethyl alcohol.

*3-Phenyl*iso*coumarin.* 3-Phenyl*iso*coumarin (1 g.) (Gabriel, *Ber.*, 1885, **18**, 2445) in benzene (30 c.c.) was exposed to sunlight for 25 days (November) and the crystals which separated were filtered off and washed several times with ether. A further quantity of the crude product was obtained on concentrating the benzene filtrate and allowing it to cool slowly to room temperature. The *photodimer* (IV) recrystallised from benzene in colourless crystals, m. p. 254° (yield almost quantitative) (Found : C, 80·7; H, 4·7. $C_{30}H_{20}O_4$ requires C, 81·1; H, 4·5%).

The photodimer was heated as described previously at 300° for 30 minutes and then left to cool in a vacuum, and the crystals of 3-phenyl*iso*coumarin (m. p. and mixed m. p.), which formed on the upper parts of the vessel, recrystallised from dilute alcohol.

Benzylidenephthalide. Benzylidenephthalide (*ca.* 1·5 g.) (Gabriel, *Org. Synth.*, Vol. XIII, 10) in benzene (25 c.c.) were exposed to sunlight for 10 days (January). The small amount of colourless crystals which separated was filtered off. The benzene filtrate was concentrated, left to cool slowly, and, while still warm treated with a few drops of ether. On cooling in ice, a colourless crystalline solid separated out, having m. p. *ca.* 206°. For purification, the *dimer* was treated again similarly with benzene–ether and then had m. p. 202—215° [Found : C, 81·6; H, 4·3%; *M* (Rast), 507. $C_{30}H_{20}O_4$ requires C, 81·1; H, 4·5%; *M*, 445].

The photodimer was heated at 260° for 40 minutes under reduced pressure. Oily drops of benzylidenephthalide (m. p. and mixed m. p.) which accumulated on the upper parts of the reaction vessel solidified on cooling slowly under reduced pressure. They were recrystallised from benzene.

Photoreactions.—2 : 7-Dimethylphenanthraquinone and stilbene. 2 : 7-Dimethylphenanthraquinone (0·5 g.) (Lieberman, *Ber.*, 1911, **44**, 1453) and stilbene (0·4 g.) in benzene (20 c.c.) were exposed to sunlight for one week in May. The benzene solution was then filtered and concentrated almost to dryness, and a small amount of hot acetone was added, followed by a few drops of methyl alcohol. A yellow solid separated on cooling (in the ice-chest) and was recrystallised from xylene. The addition *product* (V) formed almost colourless crystals which decomposed at about 258° to an orange-brown melt. It gave no colour with cold concentrated sulphuric acid, but on gentle warming a violet colour was observed (Found : C, 86·0; H, 5·3. $C_{30}H_{24}O_2$ requires C, 86·5; H, 5·7%).

Phenanthraquinone and 1 : *2-di-4′-pyridylethylene.* Phenanthraquinone (1 g., 1 mol.), and 1 : 3-di-4′-pyridylethylene (1 mol.) in benzene (30 c.c.) were exposed to sunlight in November. After 7 days, the crystals which separated were filtered off and washed with hot acetone, in which the initial components were soluble. The colouless residue of the *adduct* (VI) obtained was washed with 5% sodium hydroxide solution, then with alcohol, and lastly with ether, and decomposed at *ca.* 187° to an orange melt (Found : C, 79·4; H, 4·6; N, 7·7. $C_{26}H_{18}O_2N_2$ requires C, 80·0; H, 4·6; N, 7·2%).

Phenanthraquinone and 3 : *4-diphenyl*iso*coumarin.* Phenanthraquinone (0·7 g.) and 3 : 4-diphenyl*iso*coumarin (1 g.) (Koelsch and Le Claire, *J. Amer. Chem. Soc.*, 1943, **65**, 754) were exposed to sunlight in benzene (50 c.c.) for 20 days (December). The benzene solution was filtered, concentrated, and left to cool slowly, almost colourless crystals of the addition *product* (VIII) separating. These recrystallised from benzene in colourless crystals which decomposed at *ca.* 267° to a reddish brown melt. They gave no colour reaction with concentrated sulphuric acid, and were insoluble in cold or warm sodium hydroxide solution (*ca.* 5%) (Found : C, 83·1; H, 4·7. $C_{35}H_{22}O_4$ requires C, 83·0; H, 4·3%).

(VIII) was heated under reduced pressure (water-pump vacuum) at 300° (bath temperature) for 15 minutes in a test tube and then allowed to cool in a vacuum. The crystals formed on the upper parts of the reaction vessel were extracted with cold benzene, the benzene extract was evaporated to dryness, and the residue dissolved in the least amount of hot methyl alcohol and allowed to cool slowly. The crystals which separated proved to be 3 : 4-diphenyl*iso*coumarin. The orange crystals left undissolved after benzene extraction were recrystallised from boiling benzene and proved to be phenanthraquinone (m. p. and mixed m. p.).

*Phenanthraquinone and 3-phenyl*iso*coumarin.* Phenanthraquinone (1 g.) and 3-phenyl*iso*coumarin (1·1 g.) in benzene (30 c.c.) were exposed to sunlight for 2 days (May). A heavy crystalline deposit of *adduct* (VII) began to separate after a few hours. This was filtered off and recrystallised from xylene in almost colourless crystals decomposing to a reddish-brown melt at about 270° and giving no colour reaction in sulphuric acid (Found: C, 80·8; H, 4·3. $C_{28}H_{18}O_4$ requires C, 80·9; H, 4·2%).

(VII) was heated as was (VIII). The crystals formed on the upper parts of the reaction vessel were extracted several times with cold methyl alcohol; uniform orange crystals melting at 195° were left and gave, with concentrated sulphuric acid, the olive-green colour reaction of phenanthraquinone. On concentration of the methyl-alcoholic extract, crystals which separated out proved to be 3-phenyl*iso*coumarin (m. p. and mixed m.p.).

Phenanthraquinone and 1 : 3-*diphenyl*iso*chromen.* Phenanthraquinone (0·25 g.) and 1 : 3-diphenyl*iso*chromen (0·3 g.) (Schmidlin and Bannus, *Ber.*, 1912, **45**, 3202) partly suspended in benzene (30 c.c.) were exposed to sunlight for one week (May). The benzene solution was filtered, concentrated to small volume, and treated with light petroleum (b. p. 60—80°), which caused precipitation. The supernatant fluid was decanted, and the residual *adduct* (IX) washed with cold alcohol and recrystallised from benzene–acetone. It recrystallised from xylene in colourless crystals, decomp. *ca.* 300° to a reddish-brown melt (Found: C, 85·4; H, 5·3. $C_{35}H_{24}O_3$ requires, C, 85·3; H, 4·9%).

Photoreductions.—o-*Dibenzoylbenzene.* *o*-Dibenzoylbenzene (1·3 g.) (Simonis and Remmert, *Ber.*, 1915, **48**, 206) in *iso*propyl alcohol (30 c.c.) was exposed to sunlight for 30 days (April). The yellow crystals formed were filtered off from the fluorescent benzene solution and recrystallised from chloroform in yellow needles m. p. *ca.* 160°. They gave no colour reaction with concentrated sulphuric acid (*o*-dibenzoylbenzene gives a red colour), but in chloroform solution a green fluorescence was noted. The photo-product was heated under reduced pressure (oil-pump vacuum) in a Pyrex test-tube at 200° (bath temperature) for 1 hour and then allowed to cool slowly in a vacuum. After 24 hours a crystalline mass appeared near the bottom of the reaction vessel (most of the material used) and some yellow crystals on the upper part, which was not in contact with the bath. The lower crystalline mass recrystallised from alcohol in yellow crystals which proved to be 1 : 3-diphenyl*iso*benzofuran (XI) (m. p. and mixed m. p.) (80% yield). Both the decomposition product and an authentic specimen gave a red colour with concentrated sulphuric acid, fugitive at room temperature. The decomposition product gave the brilliant green fluorescence described by Guyot and Catel (*Compt. rend.*, 1905, **140**, 1349).

*Phenanthraquinone monoxime.** The oxime (0·5 g.) in *iso*propyl alcohol (25 c.c.) was exposed to sunlight for a fortnight (June). The brown deposit was filtered off and crystallised from 2-methylnaphthalene in very small brown crystals showing a green lustre; on pulverisation a brown powder was produced. It gave the characteristic blue colour of diphenanthro-oxazine with concentrated sulphuric acid and had m. p. above 305° (Found: N, 4·0. Calc. for $C_{28}H_{17}ON$: N, 3·7%) (yield, almost quantitative).

Phenanthraquinone imine. The experiment was carried out as previously described and the product (almost quantitative yield) crystallised from 2-methylnaphthalene in very small brown crystals showing a green lustre, giving a brown powder on pulverisation and the characteristic blue colour with concentrated sulphuric acid, and having m. p. above 305° (Found: N, 4·2. Calc. for $C_{28}H_{17}ON$: N, 3·7%).

Photochemical Reaction between Aldehydes and Phenthraquinone Monoxime.—*With benzaldehyde.* Phenanthraquinone monoxime (0·5 g.) and benzaldehyde (1 g.) in benzene (25 c.c.) were exposed to sunlight for 15 days (May) (in a Monax glass vessel); a colourless deposit was formed which was filtered off. The solution was concentrated under reduced pressure and the product recrystallised from benzene in almost colourless crystals, m. p. 256° (decomp.) depending on the rate of heating.

In a parallel experiment in the absence of light phenanthraquinone monoxime was recovered unchanged almost quantitatively.

When the photo-product was heated in a boiling ethyl cinnamate bath (b. p. 271°) in a carbon dioxide atmosphere for ½ hour, a colourless crystalline sublimate was obtained which proved to be 2-phenylphenanthro-oxazole, m. p. 204° undepressed on admixture with an authentic specimen prepared according to Stein and Day (*J. Amer. Chem. Soc.*, 1942, **64**, 2567).

With anisaldehyde. The oxime (0·5 g.) and aldehyde (1 g.) in benzene (25 c.c.) were exposed to sunlight (Monax glass vessel) for one week (April). The colourless deposit, recrystallised from absolute ethyl alcohol, had m. p. 244°, gave a yellowish-brown colour with concentrated sulphuric acid, and, when heated in an ethyl cinnamate bath, as described in the case of benzaldehyde, gave an almost colourless crystalline sublimate of 2-p-*methoxyphenylphenanthro-oxazole* (X; R = C_6H_4·OMe-*p*), m. p. 178° (Found: C, 80·9; H, 4·7; N, 4·4. $C_{22}H_{15}O_2N$ requires C, 81·2; H, 4·6; N, 4·3%).

This oxazole was also prepared as follows: Equimolecular amounts of phenanthraquinone imine and anisaldehyde (freshly distilled), dissolved in absolute alcohol containing few drops of piperidine, were refluxed for 1 hour. On cooling (and if necessary concentration of the solution) a deposit was formed which, crystallised from alcohol, had m. p. 178°, not depressed on admixture with the substance obtained as above.

o-(1 : 3-*Diketoindanyl-2-glyoxyloyl*)*benzoic Acid* (XXI).†—(XXI) was prepared from bisindane-1 : 3-dionyl (XIX) according to the directions given by Gabriel and Leupold (*loc. cit.*) for the preparation of the supposed (XVII).

Pyrolysis was carried out in a boiling-tube, connected with a vacuum pump, the lower part being immersed in a bath at 250°; the heating was for 30 minutes. Crystals of (XXII) were formed on the cold parts of the reaction vessel; they recrystallised from acetic acid in orange needles, m. p. 222—225°, undepressed on admixture with an authentic sample (cf. *loc. cit.* and Radulescu, *loc. cit.*) (Found: C, 70·8; H, 2·7. Calc. for $C_{18}H_8O_5$: C, 71·0; H, 2·6%) (yield about 40%).

A suspension of (XXI) (0·5 g.) in dilute sulphuric acid (20 c.c. of concentrated acid in 100 c.c. of water) was heated on a water-bath for 3 hours. The reaction mixture was concentrated to about 50 c.c., whereupon a yellow substance (A) separated from the solution (B). (A) recrystallised from ethyl alcohol as pale yellow needles, m. p. 208° (brown melt), and was proved to be the 2-(3-ketoindan-1-ylidene)-

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* The experiments with phenanthraquinone monoxime and imine were carried out by William Ibrahim Awad.

† These experiments were carried out by Radwan Moubasher.

indane-1 : 3-dione (XXV) by m. p. and mixed m. p. determinations with an authentic specimen prepared according to Wislicenus and Kötzle (*loc. cit.*). It dissolved in concentrated sulphuric acid, giving an orange colour. (B) was heated for 30 minutes on the water-bath, allowed to cool and filtered; and the filtrate was extracted several times with ether, from which colourless crystals were then obtained; recrystallised from ether in colourless needles, m. p. 145° (decomp.), they proved to be phthalonic acid (XXIII) (m. p. and mixed m. p.).

Di-(2-hydroxy-1 : 3-diketoindan-2-yl) (XVII).—Hydrindantin (XVIII) (1 g.) was refluxed with oxalyl chloride (10 g.) for 10 minutes, with a calcium chloride safety tube. The reaction product was evaporated to dryness in a vacuum, moisture being excluded, and the residue crystallised from benzene (anhydrous); colourless crystals were obtained, having m. p. *ca.* 235° (decomp.). The *product* (XVII) gave an orange-yellow colour with concentrated sulphuric acid (Found: C, 66·9; H, 3·3. $C_{18}H_{10}O_6$ requires C, 67·1; H, 3·1%).

The product, suspended in ether, was shaken at room temperature with water for about 30 minutes; the solid was then collected and proved to be (XVIII). (XVII) and (XVIII) are decomposed by alkali with the formation of a blue solution, containing probably the salt of the enolic form of 2-hydroxyindane-1 : 3-dione and the hydrate of (XIV) (ninhydrin).

The authors thank Dr. H. I. Thayer, Pittsburgh, Pa., for the gift of 1 : 2-di-4′-pyridylethylene.

FACULTY OF SCIENCE, FOUAD I UNIVERSITY,
ABBASSIA, CAIRO, EGYPT.

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84. *Studies in Light Absorption. Part IX. The Relation between Absorption Intensities and Molecular Dimensions, and its Application to the Electronic Spectra of Polyenes and Polycyclic Benzenoid Hydrocarbons.*

By E. A. BRAUDE.

The maximum possible extinction coefficients of molecules can be calculated in a simple manner from the molecular dimensions (cf. Braude, *Nature*, 1945, **155**, 753). The actual extinction coefficients for allowed transitions can be calculated from considerations of the effective "chromophore area" and the polarisation direction of the light absorbed. The values thus obtained for polyenes and polycyclic benzenoid hydrocarbons are in good agreement with those observed.

THE intensities of molecular spectra have received increasing attention within recent years from the experimental as well as from the theoretical point of view. On the one hand, the accurate determination of absorption intensities has become an essential feature of the development of absorption spectroscopy as an analytical tool; and, on the other, the calculation of extinction coefficients by the methods of wave mechanics has been attempted by several authors (Mulliken, *J. Chem. Physics*, 1939, **7**, 14, 20, 339, 353, 356, 364, 570; Sklar, *ibid.*, 984; *Rev. Mod. Physics*, 1942, **14**, 232; Bayliss, *J. Chem. Physics*, 1948, **16**, 287; Kuhn, *Helv. Chim. Acta*, 1948, **31**, 1780; Coulson, *Proc. Physical Soc.*, 1948, **60**, 257). These calculations, whilst of great value in helping to establish the nature of the transitions involved, have not been entirely successful quantitatively since they involve the experimental frequency of the absorption band and lead to absorption-intensity values which generally differ in order of magnitude from those observed unless empirical correction factors are introduced.

The present paper sets out a theory of absorption intensities based solely on considerations of molecular geometry, an approach which appears to have been entirely neglected in the past. It is possible to calculate, in a very simple manner, the maximum possible extinction coefficient of a molecule, the only assumption being that the light must fall within the space of the molecular dimensions in order to be absorbed. Such a calculation is quite independent of the nature of the transition or the frequency of the light. Consider light of intensity I falling on a slice of thickness δl of a cell of unit area filled with the vapour or a dilute solution in a transparent solvent of the absorbent at a concentration of c g.-mol./l. Let the average cross-sectional area of the molecule in the plane perpendicular to the direction of the incident light be $[a]$ and let the thickness of the slice be sufficiently small so that there is no superposition of molecules in the direction of propagation of the light. Then we have

$$\text{Illumination falling on molecules} = (\text{area of molecules/total area}) \times \text{total illumination} = cN[a]\delta l \,.\, I \times 10^{-3}$$

where N is the Avogadro number. Assuming that all the illumination falling on the molecules is absorbed

Illumination absorbed $= -\delta I = cN[a]\delta l \,.\, I \times 10^{-3}$
Integrating this between the limits $l = 0$ and $l = l$

$$[\varepsilon] = 1/cl \,.\, \log_{10}(I_0/I) = 0{\cdot}4343N[a] \times 10^{-3} = 2{\cdot}62 \times 10^{20}[a] \quad . \; . \; . \; . \; . \; . \quad (1)$$

where $[\varepsilon]$ is the maximum extinction coefficient. For simple molecules, $[a]$ will be of the order of 10 A.^{2}, *i.e.*, 10^{-15} cm.^{2}, so that $[\varepsilon] \sim 10^5$. This result corresponds in order of magnitude to the highest extinction coefficients which have been observed (cf. below).

According to classical theory, the absorption intensity is determined by the "oscillator strength" (f), *i.e.*, the number of oscillating units per molecule. For electronic transitions

$$f = 2{\cdot}3 \times 10^3 mc^2/N\pi e^2 \times \int\varepsilon d\nu = 4{\cdot}32 \times 10^{-9}\int\varepsilon d\nu . \quad . \; . \; . \; . \; . \; . \; . \quad (2)$$

where m and e are the mass and charge of the electron, c is the velocity of light, and $\int\varepsilon d\nu$ is the integrated band area (Ladenburg, *Verh. d. physikal. Ges.*, 1914, **16**, 769; *Z. Physik*, 1921, **4**, 451; *Physical Rev.*, 1933, **43**, 320; Mulliken, *J. Chem. Physics*, 1939, **7**, 14; Förster, *Z. Elektrochem.*, 1939, **45**, 548). Approximately, $\int\varepsilon d\nu = \varepsilon_{\max.}\Delta\nu$ where $\Delta\nu$ is the "half-width," *i.e.*, the width of the bands at points where $\varepsilon = \frac{1}{2}\varepsilon_{\max.}$. $\Delta\nu$ is usually of the order of 5000 cm.$^{-1}$ and for $f = 1$, equation (2) gives $\varepsilon \sim 10^5$. The present treatment thus leads to the same general result as the classical one.

In considering the application of the chromophore-area theory to particular molecules and transitions, at least four factors must be taken into account which will generally reduce the actual extinction coefficient ε considerably below the maximum possible coefficient $[\varepsilon]$. First, in polyatomic molecules the effective chromophore area a will generally be smaller than the maximum cross-sectional area $[a]$ because a given electronic or vibrational transition will be confined to a particular atom or group of atoms and only light falling within the space of the atoms and bonds concerned will be absorbed. Secondly, vibrational and electronic transitions are polarised along a particular axis and only the electric vector of the light in that axis will be effective. For randomly orientated molecules, the statistical factor by which the effective incident intensity, and therefore ε, is reduced, is $\frac{1}{3}$. Thirdly, the ground state of the molecule is usually distributed over a number of vibrational states, and in some cases, over more than one electronic state, and if the transition ouly take place from a particular sub-level or -levels, the extinction coefficient for a photon of a given magnitude (wave-length) will be further reduced by a fraction (χ) corresponding to the fractional population of the sub-level or -levels concerned. Fourthly, even when other necessary conditions are fulfilled, the interaction probability (κ) may be less than unity. Hence

$$\varepsilon = \kappa \times \chi \times \tfrac{1}{3} \times 2{\cdot}62 \times 10^{20}a = \kappa \times \chi \times 0{\cdot}87 \times 10^{20}a \quad . \; . \; . \; . \; . \; . \quad (3)$$

In the sequel, discussion will be confined to electronic transitions and we shall assume $\chi = 1$. We shall also assume that, for an *allowed* electronic transition, $\kappa = 1$. Hence

$$\varepsilon = 0{\cdot}87 \times 10^{20}a \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (3a)$$

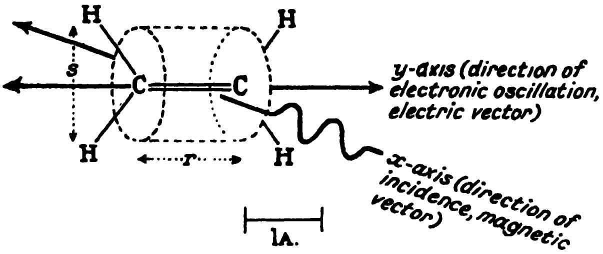
This extremely simple expression for ε involves only one other parameter, the chromophore area a, and should hold for any allowed electronic transition. On this basis the problem of calculating the absorption intensities due to such transitions therefore reduces to the calculation of the chromophore area a.

The application of (3a) can be well illustrated in the polyene and polycyclic hydrocarbon series. The electronic spectra of these have been thoroughly investigated experimentally, and quantitative data for the parent compounds, ethylene and benzene, have recently become available through the work of Klevens, Platt, and their collaborators in the vacuum-ultraviolet region. It is known that the absorption of ethylenic molecules in the visible and ultraviolet regions is due to transitions of the unsaturation (π) electrons. The effective chromophore area a will correspond to the area occupied by the π-electrons (or, more precisely, the area containing a sufficiently high π-electron density) in the plane perpendicular to the line of propagation (magnetic vector) of the light. In order to calculate a it is necessary to know the polarisation direction of the transition since the cross-sectional area will be different in different axes of the elongated polyene and flat polycyclic-hydrocarbon molecules. It is generally accepted on the basis of molecular-orbital theory that the polarisation direction (electric vector) of transitions involving π-electrons is along the axis of the bond, corresponding to a classical direction of incidence (magnetic vector) at right angles to the bond (cf. Bowen, *Ann. Reports*, 1943, **40**, 12).

The polarisation direction can also be deduced from a consideration of chromophore area and the experimentally observed relationship between chain-length and extinction coefficient in the polyene hydrocarbons, taking into account their elongated zig-zag (*trans*)-configuration. Calling the short and long axes of the molecule x and y, if the electronic oscillation takes place along the x-axis, the required classical direction of incidence of the light would be along the y-axis, and the effective cross-sectional area would be approximately independent of the length of the polyene chain and the number (n) of ethylenic bonds. Hence, by (3a), ε should be largely independent of n. If, on the other hand, the electronic oscillation takes place along the y-axis, *i.e.*, along the axis of the ethylenic bonds, the required classical direction of incidence of the light will be along the x-axis, and the effective cross-section of the molecule will increase with the length of the polyene chain. Hence by (3a), ε should also increase with n. This is the relationship experimentally observed (cf. Hausser, Kuhn, and Smakula, *Z. physikal. Chem.*, 1935, **29**, *B*, 385). On the present interpretation, the increase in ε with increasing length of the polyene chain is therefore simply due to the concomitant increase in chromophore area It will be noted that the deduced polarisation direction is here quite independent of the numerical magnitude of the extinction coefficients but follows directly from the qualitative relationship between ε and n.

FIG. 1.

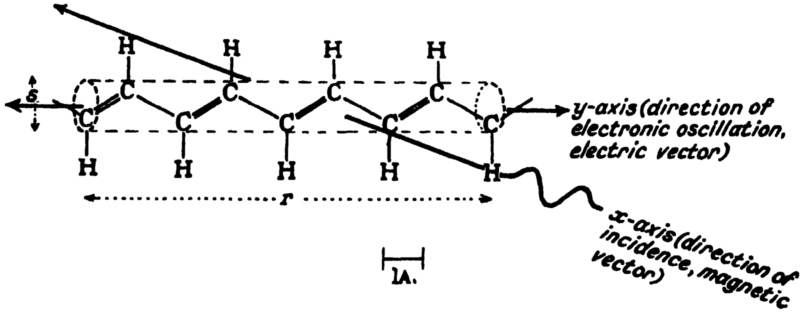
Absorption of light by ethylene ($\lambda_{max.}$ *ca.* 1650 A.).


H
H
s
C
C
H
H
r
y-axis (direction of electronic oscillation, electric vector)
x-axis (direction of incidence, magnetic vector)
1A.

The required direction of incidence for the transitions under discussion having been established, the chromophore area can readily be estimated. Considering first the parent compound, ethylene, it is clear that the space containing an appreciable π-electron density will be considerably smaller than the total space occupied by the molecule; the carbon–hydrogen bonds have no, or very little, double-bond character and the π-electrons can be regarded as confined to the immediate neighbourhood of the carbon–carbon link. For simplicity, they may be imagined to occupy a cylinder of length r and diameter s (Fig. 1) formed by the lateral coalescence of the lobes representing the spatial distribution of the p-electrons of the two carbon atoms (cf. Coulson, *Quarterly Reviews*, 1947, **1**, 144). The effective dimensions of the cylinder will depend on the π-electron density required for interaction with a photon. (More precisely, there will be a region in which the interaction probability is unity, or, at any rate, approximately constant, and beyond which κ rapidly falls.) It is reasonable to assume that the necessary electron-density will be of the same order as the electron-density required for interaction with X-rays, and r may therefore be put equal to the carbon–carbon double-bond length 1·35 A.,

FIG. 2.

Absorption of light by polyenes ($\lambda_{max.}$ 2000—5000 A.).


H
H
H
H
s
C
C
C
C
C
C
C
C
H
H
H
H
H
r
y-axis (direction of electronic oscillation, electric vector)
x-axis (direction of incidence, magnetic vector)
1A.

whilst s may be estimated from X-ray contour diagrams for substituted ethylenes (*e.g.*, stilbene, Robertson and Woodward, *Proc. Roy. Soc.*, 1937, **162**, *A*, 568) to be about 1·5 A. The required chromophore area will be the rectangular cross-section of the cylinder, *i.e.*, $a = 1{\cdot}35 \times 1{\cdot}5 = 2$ A.^{2}, whence, by (3a), $\varepsilon = 17{,}400$. The experimental value, recently determined by Platt, Klevens, and Price (*J. Chem. Physics*, 1949, **17**, 466) is $\varepsilon = 15{,}000$. The agreement is closer than might be expected in view of the approximations involved in the estimation of a.

In butadiene and the higher members of the polyene series, the conventional carbon–carbon single bonds are known to possess appreciable double-bond character and the π-electron density is distributed over the whole chain of carbon atoms. For simplicity, the π-electrons may again be regarded as occupying a cylinder of diameter 1·5 A. and of length corresponding to the distance r between the terminal carbon atoms, taking into account the zig-zag *trans*-configuration of the polyene chain (cf. Bayliss, *J. Chem. Physics*, 1948, **16**, 287) (Fig. 2). The chromophore area is then given by $1{\cdot}5r$ A.^{2}, and, by (3a), $\varepsilon = 1{\cdot}31 \times 10^{20}\, r$. The calculated and observed values are shown in the Table. It will be seen that $\varepsilon_{\text{obs.}}$ is always somewhat smaller than $\varepsilon_{\text{calc.}}$ on this basis and that the ratio $\varepsilon_{\text{obs.}}/\varepsilon_{\text{calc.}}$ decreases with n. Nevertheless, the agreement is very satisfactory considering the approximate method of estimating a; some reasons for the discrepancies are further considered below.

Calculated and observed molecular-extinction coefficients for polyenes and polycyclic hydrocarbons.

$\varepsilon_{\text{calc.}}^{(1)} = 1{\cdot}31 \times 10^{20}\, r$. $\varepsilon_{\text{calc.}}^{(2)} = 1{\cdot}74 \times 10^{20}\, n$ for polyenes and polycyclic hydrocarbons, $\varepsilon_{\text{calc.}}^{(2)} = 1{\cdot}74 \times 10^{20}\, (n + 1)$ for diphenylpolyenes.

	$\varepsilon_{\text{obs.}}$	r, A.[1]	$\varepsilon_{\text{calc.}}^{(1)}$	$\varepsilon_{\text{obs.}}/\varepsilon_{\text{calc.}}^{(1)}$	$\varepsilon_{\text{calc.}}^{(2)}$	$\varepsilon_{\text{obs.}}/\varepsilon_{\text{calc.}}^{(2)}$
		$H{\cdot}[CH = CH]_n{\cdot}H$.				
$n = 1$	15,000 [2]	1·35	17,400	0·86	17,400	0·86
2	21,000 [3]	3·66	48,000	0·44	34,800	0·60
3	53,000 [4]	6·14	81,000	0·65	52,200	1·01
4	64,000 [3]	8·62	113,000	0·57	69,600	0·92
5	51,000 [3]	11·10	145,000	0·34	87,000	0·59
6	70,000 [3]	13·6	178,000	0·39	104,000	0·67
11	65,000 [3]	26·0	340,000	0·19	191,000	0·34
		$Ph{\cdot}[CH = CH]_n{\cdot}Ph$.				
$n = 1$	27,000 [4]	3·68	47,000	0·57	34,800	0·78
2	41,000 [4]	6·16	81,000	0·51	52,200	0·78
3	65,000 [4]	8·64	114,000	0·57	69,600	0·93
4	90,000 [4]	11·1	145,000	0·62	87,000	1·03
5	94,000 [4]	13·6	178,000	0·53	104,000	0·90
6	117,000 [4]	16·1	210,000	0·56	122,000	0·96
7	135,000 [4]	18·6	242,000	0·56	139,000	0·97
Benzene ($n = 3$)	46,000 [2]	—	106,000	0·44	52,200	0·88
Naphthalene ($n = 5$)	133,000 [5]	—	176,000	0·76	104,000	1·28
Anthracene ($n = 7$) ...	180,000 [5]	—	248,000	0·72	122,000	1·50
Naphthacene ($n = 9$)...	180,000 [6]	—	320,000	0·56	157,000	1·14

[1] Bayliss, *J. Chem. Physics*, 1948, **16**, 287. [2] Platt, Klevens, and Price, *ibid.*, 1949, **17**, 466. [3] Data taken from Braude, *Ann. Reports*, 1945, **42**, 105. The data for $n > 3$ refer to alkyl-substituted polyenes. [4] Hausser, Kuhn, and Smakula, *Z. physikal. Chem.*, 1935, **29**, *B*, 385. [5] Mayneord and Roe, *Proc. Roy. Soc.*, 1935, **152**, *A*, 299. [6] Klevens and Platt, *J. Chem. Physics*, 1949, **17**, 470.

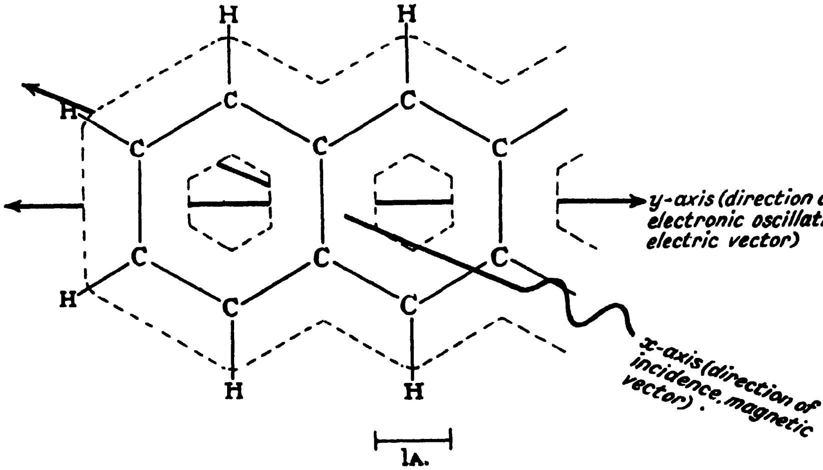
In the diphenyl polyenes, the total area containing π-electrons is increased by the terminal phenyl groups, but it is reasonable to assume that transitions involving the polyene chain will only be produced by photons striking the central, acyclic part of the molecule, whereas in the region of the phenyl groups the interaction probability for such transitions will be small. (This is in agreement with molecular-orbital calculations which indicate that the effective length of the conjugated system corresponds to the acyclic portion, cf. Bayliss, *loc. cit.*) Thus, for calculating extinction coefficients of the high-intensity, long-wave-length bands of the diphenylpolyenes, the chromophore area can be taken as approximately the same as for the corresponding unsubstituted polyenes with one extra ethylenic group. The values thus obtained (see Table) are in good agreement with those observed, the ratio $\varepsilon_{\text{obs.}}/\varepsilon_{\text{calc.}}$ falling consistently within the range 0·5—0·6 for $n = 1$—7.

Benzene exhibits three absorption bands, near 2550, 2000, and 1800 A., ascribed to transitions involving the system of π-electrons. The first two of these are of relatively low intensity and are assigned to "forbidden" transitions, but the 1800 A.-band is of high intensity and must be due to an "allowed" transition (Platt and Klevens, *Chem. Reviews*, 1947, **41**, 301; *J. Chem.*

Physics, 1948, **16**, 832; 1949, **17**, 470; Platt, *ibid.*, p. 484). Similar high-intensity bands of increasing wave-lengths and intensities are exhibited by the higher polycyclic hydrocarbons, and with the first three or four members of the series, the extinction coefficients are approximately proportional to the number of carbon atoms. This means that, as in the acyclic polyenes, the chromophore area also increases approximately linearly with the size of the molecule and indicates that the effective direction of incidence of the light absorbed is at right angles to the plane of the rings, and hence that the electric vector of the transitions lies *in* the plane of the rings (Fig. 3). This is in agreement with molecular-orbital theory (cf. Coulson, *loc. cit.*), and the same has been shown experimentally to apply to the low-intensity bands (Krishnan, *Proc. Indian Acad. Sci.*, 1938, **8**, 487; Scheibe, *Naturwiss.*, 1939, **8**, 478; Scheibe, Hartwig, and Müller, *Z. Elektrochem.*, 1943, **49**, 372). Since the π-electrons are equally distributed over all six carbon–carbon bonds, the chromophore area of benzene will therefore be approximately six times as great as that of ethylene, if any effect due to the thinning-out of the electron density is neglected. Similarly, for the higher members, the chromophore area and $\varepsilon_{\text{calc.}}$ will, on this basis, be equal to that of the acyclic polyene with the same number of carbon atoms. As before, the agreement between $\varepsilon_{\text{calc.}}$ and $\varepsilon_{\text{obs.}}$ is quite satisfactory (see Table). The calculated values are larger than those observed by factors up to about 2. Moecular-orbital calculations for this type of molecule, on the other hand, predict intensities which are smaller than those observed by factors of the order of 10 (Coulson, *Proc. Physical Soc.*, 1948, **60**, 257).

Fig. 3.

Absorption of light by benzenoid hydrocarbons (allowed electronic transition).


H
H
H
C
C
C
C
C
C
C
C
C
C
H
H
H
y-axis (direction of electronic oscillation, electric vector)
x-axis (direction of incidence, magnetic vector).
1Å.

In the preceding discussion of acyclic and cyclic polyenes, the chromophore area has been taken to be proportional to the total number of carbon–carbon bonds in the polyene chain. This involves the assumption that the partial double-bond character of the conventional single carbon–carbon bonds is sufficient to render them as effective as the conventional double bonds for interaction with photons giving rise to π-electron transitions, and, similarly, that the " thinning-out " of the π-electron cloud will not appreciably reduce the effectiveness of the conventional double bonds for interaction with photons. The extent to which these assumptions are justified will depend on the exact relationship between π-electron density and interaction probability, concerning which little is known. An alternative approximation to the above is to assume that the effective chromophore area will be proportional to the *total* π-electron density, *i.e.*, to the number (n) of conventional ethylenic bonds. On this basis, ε should by (3a) also be directly proportional to n, and $\varepsilon_{\text{calc.}} = 0{\cdot}87 \times 10^{20}a_{\text{C=C}} \times n$, where $a_{\text{C=C}}$ is the chromophore area of an ethylenic bond, *i.e.*, $\varepsilon_{\text{calc.}} = 0{\cdot}87 \times 2 \times 10^{20}n = 1{\cdot}74 \times 10^{20}n$. The values thus obtained are in better agreement with the experimental data than those calculated previously in the case of the acyclic polyenes, but in less good agreement in the case of the aromatic hydrocarbons (see Table). This indicates that the " thinning-out " effect is more important in the acyclic than in the cyclic series, in agreement with the fact that the effective classical oscillator-strengths per π-electron are also consistently lower in polyenes than in aromatic hydrocarbons (Klevens and Platt, *J. Chem. Physics*, 1949, **17**, 470).

The fact that the observed and calculated values of ε are in fair agreement shows that the assumption made in deriving equation (3a), namely that the interaction probability is approximately unity for allowed transitions, is justified. For forbidden transitions, the interaction coefficient κ will be small and can readily be calculated from the experimental data by means of equation (3). This also provides a useful criterion of whether a transition is allowed or forbidden. Thus for the 2550-A. band of benzene, $\varepsilon_{\text{obs.}} = 200$ and $\varepsilon_{\text{calc.}} \sim \kappa \times 100{,}000$ (cf. Table), hence $\kappa = 0{\cdot}002$.

In conclusion, some other factors likely to be responsible for relatively small discrepancies between $\varepsilon_{\text{calc.}}$ and $\varepsilon_{\text{obs.}}$ may be briefly discussed. The data in the Table show that, even for the highest-intensity electronic bands, the observed extinction coefficients are generally slightly lower than those calculated by chromophore-area theory. This is not unexpected in view of the approximations made. In the first place, χ in equation (3) will generally be less than unity since polyatomic molecules usually occupy a number of vibrational levels in the ground state and consequently give rise to an absorption band of considerable width rather than an absorption line. This factor could be accounted for by comparing band areas ($\int\varepsilon d\nu$) rather than extinction coefficients (cf. Mulliken, *loc. cit.*) but the correction is not worth making as the data at present available for $\int\varepsilon d\nu$ are generally less accurate than the values of ε calculated by (3a). Secondly, apart from the intrinsic uncertainty in estimating the dimensions of the π-electron cloud, the effective chromophore area a will generally be smaller than that deduced by the simple considerations outlined above owing to intramolecular shielding effects. These are not easily amenable to quantitative treatment, but a qualitative indication of such effects is provided by the fact that $\varepsilon_{\text{obs.}}$ decreases with increasing substitution in the alkylated olefins (Klevens and Platt, *loc. cit.*). The decrease in absorption intensity usually associated with steric hindrance has been interpreted (Part VI, Braude, Koch, Jones, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890) as partly due to a decrease in the population of the active vibrational levels, *i.e.* to a decrease in χ, but it is probable that shielding effects are also operative in such cases. The abnormally low value of $\varepsilon_{\text{obs.}}$ in some natural polyenes, *e.g.*, γ-carotene ($n = 11$, see Table) is probably due to similar causes and also suggests the possibility that compounds of this type may not possess the all-*trans*-configuration which has been postulated (Zechmeister, *Chem. Reviews*, 1944, **34**, 267).

Chromophore area considerations are, of course, in no way limited to transitions involving π-electrons, but are equally applicable to other electronic and to vibrational spectra. However, hardly any quantitative extinction measurements in the far ultra-violet or infra-red regions are at present available.

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Imperial College of Science and Technology,
London, S.W.7.

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85. *Cinnolines. Part XXV. Experiments with 3-Halogeno-4-hydroxycinnolines. Some Halogen Exchange Reactions.*

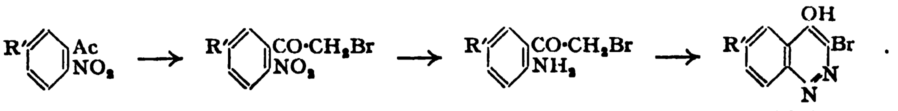
By K. Schofield and T. Swain.

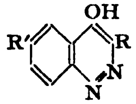
The bromination of diazotised *o*-aminoacetophenone, and the bromination and chlorination of 4-hydroxycinnoline, have given mediocre yields of 3-halogeno-4-hydroxycinnolines. The substitution of bromine by chlorine which occurs when bromo-4-hydroxycinnolines react with phosphorus chlorides appears to proceed by different mechanisms, depending on the presence of the bromine at $C_{(3)}$ or $C_{(6)}$. Qualitative comparison with related 4-hydroxyquinolines shows that these undergo chlorination and bromination more rapidly and more efficiently at $C_{(3)}$ than do analogous cinnolines, but halogen exchange reactions occur much more slowly, if at all.

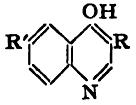
The synthesis of some 3-halogeno-4-hydroxycinnolines (I; R = Cl or Br, R′ = H, Cl or Br) was recently reported (Schofield and Simpson, *J.*, 1948, 1170). Some experiments with these compounds and a qualitative comparison with analogous quinoline derivatives are now described.

The original synthesis of 3-bromo-4-hydroxycinnolines (II ⟶ IV) suffers from the disadvantages, especially in the case of (II; R′ = H), that pure nitroacetophenones are essential, and that compounds (III) are unstable. Thus, before beginning a study of 3-bromo-

4-hydroxycinnolines, some experiments were made in search of a simplified route to these compounds. The results are of interest, but it cannot be claimed that the desired products have been rendered any easier of access.


(II.) (III.) (IV.)


(I.)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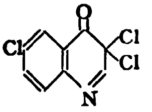
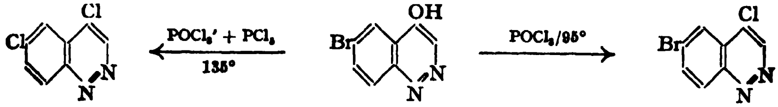

(VI.)

Bülow and Schmachtenberg (*Ber.*, 1908, **41**, 2607) found that the decomposition of benzenediazonium perbromide in the presence of acetophenone gave ω-bromoacetophenone, and Hopf and Le Fèvre (*J.*, 1939, 1067) also observed the brominating action of a compound of this type. It seemed possible, therefore, that decomposition of the perbromide from diazotised *o*-aminoacetophenone might provide 3-bromo-4-hydroxycinnoline, obviating the need for pure *o*-nitroacetophenone, *o*-aminoacetophenone being available from the crude nitro-compound arising from the nitration of acetophenone (Schofield and Swain, *J.*, 1948, 384). Under a variety of conditions 3-bromo-4-hydroxycinnoline was obtained by this method. In no case was the yield greater than 34%, but the experiments were not exhaustive and the reaction might repay further study.

Direct halogenation of the readily available 4-hydroxycinnolines promised to be an attractive route to 3-halogeno-4-hydroxycinnolines. Examples of analogous brominations of quinoline derivatives are mentioned in the early literature (Chick and Wilsmore, *J.*, 1910, **97**, 1990; Knorr, *Annalen*, 1886, **236**, 91; Meyer and Heinmann, *Compt. rend.*, 1936, **203**, 264), and recently Riegel and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 1229, 1532) prepared 3-bromo-4-hydroxyquinolines by this method, whilst Surrey and Cutler (*ibid.*, p. 2570) made a comprehensive study of the direct halogenation of ethyl 4-hydroxyquinaldates with sulphuryl chloride, bromine, and iodine monochloride, in acetic acid, obtaining the corresponding 3-halogeno-derivatives. Consequently, we treated 4-hydroxy-, 6-chloro-4-hydroxy-, and 6-bromo-4-hydroxy-cinnoline with both sulphuryl chloride and bromine in acetic acid. In no case was halogenation so rapid or so efficient as with the related quinoline derivatives under the same conditions. The products appeared to be mixtures, from which mediocre yields (*ca.* 20%) of 3-halogeno-4-hydroxycinnolines (I; R = Cl or Br; R′ = H, Cl or Br) were isolated.

For comparative purposes, and because the products were required for the work described later in this paper, the quinoline analogues (V; R = Cl or Br, R′ = H, Cl or Br) of the above cinnolines were prepared. 4-Hydroxy- and 6-chloro-4-hydroxy-quinoline are readily prepared by the ethoxymethylenemalonic ester reaction (see, among others, Price and Roberts, *ibid.*, p. 1204) and we have now prepared *6-bromo-4-hydroxyquinoline* by this method (see Experimental). By the action of sulphuryl chloride on 4-hydroxyquinoline we isolated a low yield of a trichloro-derivative (cf. Riegel *et al.*, *ibid.*, p. 1229). Surprisingly, this compound appeared to be converted by mixed phosphorus chlorides into a trichloroquinoline which did not depress the m. p. of 3 : 4 : 6-trichloroquinoline (see below). Although mixed m. p.s are not reliable with compounds of this type, the sequence of reactions suggests some such structure as (VI) for the initial product. With 6-chloro- and 6-bromo-4-hydroxyquinoline (in contrast to the cinnoline derivatives), sulphuryl chloride effected rapid and efficient monochlorination, giving what we regard as 3 : *6-dichloro-* and *3-chloro-6-bromo-4-hydroxyquinoline*. Bromination of the hydroxy-compounds under the conditions of Surrey and Cutler (*loc. cit.*) (Riegel *et al.*, *loc. cit.*, used a longer reaction time) proceeded rapidly enough at 95° to give good yields of *3-bromo-*, *6-chloro-3-bromo-*, and 3 : *6-dibromo-4-hydroxyquinoline* in ten minutes.

One of our objects in preparing the above halogeno-4-hydroxycinnolines was to examine further the problem of halogen exchange. In previous cinnoline studies (Schofield and Simpson, *loc. cit.*; Atkinson and Simpson, *J.*, 1947, 232; Keneford, Morley, and Simpson, *J.*, 1948, 1702) cases of the replacement of a bromine atom by a chlorine atom in the diazonium salt stage of the Borsche synthesis have been observed. But another type of replacement involving a bromine atom in a cinnoline nucleus was observed by Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419), who noticed that, although phosphorus oxychloride at 95° converted 6-bromo-4-hydroxycinnoline into 4-chloro-6-bromocinnoline, a mixture of phosphorus oxychloride and pentachloride at 135° produced a compound which they suggested was 4 : 6-dichlorocinnoline. This suggestion was readily proved correct. Morley, Keneford, and Simpson (*loc. cit.*) observed what is probably a similar replacement of the nitro-group in 7-chloro-6-nitro-4-hydroxycinnoline. Our own interest in reactions of this sort was prompted by the observation that mixed phosphorus chlorides converted 3-bromo-4-hydroxycinnoline into a product intermediate in composition between 4-chloro-3-bromo- and 3 : 4-dichloro-cinnoline. We have examined the action of phosphorus oxychloride and pentachloride, alone and mixed, at 95° and 135°, on 3-bromo-, 6-bromo-, 6-chloro-3-bromo-, and 3 : 6-dibromo-4-hydroxycinnoline.



Three criteria were used to detect and roughly estimate the occurrence of bromine replacement by chlorine. Most important was elementary analysis of the products, and of the derived 4-phenoxy-compounds. Secondly, although with these compounds mixed m. p.s are of little value since depressions are not in general observed, yet m. p.s of the products provided a useful criterion since it was found that they rose as the degree of exchange decreased. In this connection 4 : 6-dichloro- and 4-chloro-6-bromo-cinnoline, required as standard substances, were already known (Keneford and Simpson, *J.*, 1947, 917; Leonard and Boyd, *loc. cit.*), and by usual methods we prepared 3 : *4-dichloro-* and 3 : 4 : *6-trichloro-cinnoline*, and also *3-chloro-4-phenoxycinnoline*. Thirdly, if replacement was occurring, bromine appeared in the reaction vessel.

The essential results, obtained under the standard conditions used in these experiments, are summarised in Table I, from which the degree of exchange in any example can be judged roughly by the m. p. of the product, and also by the approximate calculation of percentage exchange based on the carbon content of the compounds.

It was important to decide if the 4-hydroxy-group was involved in the exchange reaction, or if its replacement by chlorine was completed before substitution of bromine by chlorine occurred. The latter possibility seemed the more likely since Leonard and Boyd (*loc. cit.*) reported that the hydroxyl group of 4-hydroxycinnoline was replaced in five minutes under the action of phosphorus oxychloride, and Surrey and Cutler (*loc. cit.*) have shown that in ten minutes the same reagent can convert many 4-hydroxyquinolines into the 4-chloro-compounds. We find that 4-chloro-, 4 : 6-dichloro-, and 3 : 4-dichloro-cinnoline are formed quantitatively in this short reaction time, and by this means it was possible to convert bromine-containing 4-hydroxycinnolines into the 4-chloro-compounds with a minimum of halogen exchange, although the products were not quite pure. Complete proof that the 4-hydroxy-group is not essential to the exchange reaction was provided by showing that further treatment of these fairly pure 4-chloro-bromocinnolines with phosphorus chlorides caused exchange of chlorine for bromine in the same way as when the 4-hydroxy-compounds were used in the reaction.

The quinoline derivatives described above provided an interesting comparison with their cinnoline analogues, when treated under the conditions which caused halogen exchange in the latter. 4 : 6-Dichloro- and 4-chloro-3-bromo-quinoline have been described by Riegel *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1264, 1229), and we have now prepared *4-chloro-6-bromo-*, 3 : 4 : *6-trichloro-*, 3 : *4-dichloro-6-bromo-*, 4 : *6-dichloro-3-bromo-*, and *4-chloro-3* : *6-dibromo-quinoline*. Treatment of the bromine-containing compounds with phosphorus chlorides, under conditions which replace, partly or completely, the bromine in the cinnoline analogues, did cause some halogen exchange (as evinced by bromine vapour appearing in the reaction vessels) but analysis showed it to have occurred to a very small extent. This was expected in view of earlier reports of the preparation of 4-chloro-compounds from bromine-substituted 4-hydroxyquinolines. Thus, Kermack and Weatherhead (*J.*, 1939, 563) boiled 6-bromo-4-hydroxyquinaldine for four hours with phosphorus oxychloride without apparently replacing the bromine atom. Steck and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 129, 380) satisfactorily prepared 4-chloro-5-, -6-, and -7-bromo-3-methylquinoline by a similar method, and Riegel *et al.* (*loc. cit.*) likewise obtained 4-chloro-3-bromoquinoline.

The conclusions to be drawn from Table I and from the above discussion can be stated briefly: (i) Replacement of the 4-hydroxy-group precedes halogen exchange and is indeed a very

TABLE I.

Summary of results obtained in halogen exchange reactions.

Conditions.				M. p.[a] and exchange, %, of products from substituted 4-hydroxy-cinnoline.							
				6-Bromo-.		3-Bromo-.		6-Chloro-3-bromo-.		3 : 6-Dibromo-.	
Re-agent.[b]	Time (hrs.).	Temp.	Reflux or open.[c]	M. p.	Ex-change, %.	M. p.	Ex-change, %.	M. p.	Ex-change, %.	M. p.	Ex-change, %.[d]
M	2	95°	O	113°	—	147°[e]	34	142·5°	100	146°	47
M	¼	95	O	126	—	—	—	—	—	—	—
M	2	95	R	—	—	143·5[e]	37	143·5[f]	83	147	47
M	2	135	O	113[g]	100[h]	149·5	7·5	149·5	51	156·5	31
M	2	135	R	—	—	153	6	154·5	14	161	10
M	24	95	R	—	—	130	—	—	—	—	—
M	24	135	R	—	—	143	—	148	—	152	—
O	2	95	R	118	—	142	—	145	—	148	—
O	2	135	R	113	—	151·5	—	152	—	159	—
P	1	95	R	126	—	127	—	140	—	—	—
P	½	135	R	—	—	130	—	135	—	141	—

(*a*) M. p.s of possible products: 3 : 4-dichlorocinnoline, m. p. 126—127°; 4 : 6-dichlorocinnoline, m. p. 112—113°; 3 : 4 : 6-trichlorocinnoline, m. p. 141—142°. (*b*) M = mixed phosphorus chlorides; P = phosphorus pentachloride; O = phosphorus oxychloride. (*c*) R = reflux; O = open vessel. (*d*) Based on total bromine (2 atoms). (*e*) This is the only case where reaction under reflux caused more exchange, but the difference is small. (*f*) 1 hour's heating. (*g*) ½ hour or 2 hours. (*h*) From Leonard and Boyd's figures (*loc. cit.*).

rapid reaction. (ii) A mixture of phosphorus oxychloride and pentachloride being used, replacement of the bromine at $C_{(6)}$ is relatively rapid, and occurs more readily at the higher of the two temperatures used. (iii) By comparison, replacement of a bromine atom at $C_{(3)}$ is relatively slow, appears to be encouraged by the presence of a halogen atom at $C_{(6)}$, and is more rapid at 95° than at 135°. (iv) Replacement of bromine, whether at $C_{(3)}$ or $C_{(6)}$, by using phosphorus pentachloride, proceeds more rapidly at the higher temperature. (v) Phosphorus oxychloride, in contrast, produces similar results to those obtained with the mixed chlorides. (vi) Generally, use of an open vessel, whence bromine can easily escape, facilitates exchange, and the reverse is true for reactions carried out under reflux. (vii) Halogen exchange in the quinoline series proceeds very much more slowly, if at all appreciably, than in the cinnoline series.

Useful discussion of these results is rendered difficult, first by the absence of true analogies, and secondly by ignorance of the mechanism of reactions between phosphorus chlorides and compounds of the present type. Several examples of the replacement of bromine atoms by chlorine, through the agency of phosphorus pentachloride, in both the benzene and the naphthalene series have been reported (Schmidt and Wagner, *Annalen*, 1912, **387**, 164; Cone and Robinson, *Ber.*, 1907, **40**, 2160; Sindall, *Chem. News*, 1890, **60**, 58), but the conditions have usually been comparatively severe. In any case, different mechanisms may be involved in these examples. At first it seemed possible that the 4-hydroxy-group might be intimately connected with exchange of the 3-bromo-atom, somewhat in the manner in which a hydroxyl group adjacent to a halogen atom in a naphthalene compound controls the subsequent mode of halogenation (Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245), but the facts presented make it clear that the hydroxyl group is in no way involved in the reaction.

The different form of temperature dependence of the substitution at $C_{(6)}$ as against $C_{(3)}$ seems to suggest that different mechanisms of replacement are operative at each position. Possibly replacement of the 6-bromo-atom is an ordinary nucleophilic substitution, and from the point of view of comparative heterocyclic chemistry it is interesting that the cinnoline compounds are more susceptible to nucleophilic replacement than are the members of the quinoline series.

The qualitative results of bromination and chlorination of 4-hydroxycinnolines and 4-hydroxyquinolines suggest, on the other hand, that in the quinoline compounds $C_{(3)}$ is more readily attacked by electrophilic reagents than $C_{(3)}$ in 4-hydroxycinnolines. This is also true of our observation that 4-hydroxycinnoline fails to partake in a Mannich reaction under conditions which produce substitution of this kind in 4-hydroxyquinoline derivatives (Price and Jackson, *J. Amer. Chem. Soc.*, 1946, **68**, 1282). It should be noted that our results do not allow us to decide if $C_{(3)}$ in 4-hydroxyquinolines is absolutely more susceptible to electrophilic substitution than $C_{(3)}$ in 4-hydroxycinnolines, or only relatively so, as compared with other positions in the two nuclei. Only a knowledge of the fate of material not accounted for as 3-halogeno-4-hydroxycinnoline, *i.e.*, whether it remained unsubstituted or whether substitution occurred at positions other than $C_{(3)}$, could decide this question.

It would clearly be of interest to examine the ease of halogen exchange in cinnolines unsubstituted at $C_{(4)}$ and this we hope to do.

EXPERIMENTAL.

(M. p.s are uncorrected.)

Bromination of Diazotised o-*Aminoacetophenone*.—(i) The amine (1 g.) in sulphuric acid (10 c.c.; 60% v/v) was diazotised at 0° with aqueous sodium nitrite (10%), and a solution of potassium bromide (1·47 g.) and potassium bromate (0·41 g.) in water (10 c.c.) added slowly at –5° to 0°. The suspension of brown granular solid produced was left overnight and then warmed at 80° for ½ hour, and the tarry resin formed crystallised twice from alcohol. 3-Bromo-4-hydroxycinnoline (0·25 g., 15%) was thus isolated as pale brown needles, m. p. 273—274°, alone and mixed with an authentic specimen (m. p. 275—276°).

(ii) *o*-Aminoacetophenone (0·5 g.) was treated as in (i) but the suspension was left for 1 week at room temperature before being worked up as before. There resulted 0·28 g. (34%) of 3-bromo-4-hydroxycinnoline, m. p. 271—272°.

(iii) The ketone (0·59 g.) was diazotised as before, treated with a solution of potassium bromide (1·18 g.) and potassium bromate (0·21 g.) in water (5 c.c.), and worked up as in (ii), yielding 20% of the desired product.

(iv) The amine (1 g.) was diazotised and treated with a solution of potassium bromide (1·24 g.) and bromine (2·04 g.) in water (10 c.c.), left overnight, and worked up as in (i), yielding 12·5% of 3-bromo-4-hydroxycinnoline.

Direct Halogenation of 4-Hydroxycinnolines.

Chlorination of 4-Hydroxycinnoline.—The cinnoline (0·5 g.) in acetic acid (20 c.c.) and acetic anhydride (1 c.c.) was warmed at 95° for 4 hours with sulphuryl chloride (0·51 g.), the mixture refluxed for 5 minutes and then cooled, sodium hydroxide (0·2 g.) in water (10 c.c.) added, and the solution left at 0° for 3 hours. Recrystallisation of the precipitate (0·24 g.; m. p. 262—263°) from acetic acid gave 3-chloro-4-hydroxycinnoline (0·14 g., 22%), m. p. 278—279°, alone and mixed with an authentic specimen (m. p. 278—279°). Acetylation with boiling acetic anhydride gave a derivative, m. p. 124—125°, which did not depress the m. p. (124—125°) of genuine 3-chloro-4-acetoxycinnoline.

Chlorination in boiling acetic acid for 4 hours gave the same result, but one experiment at 95° using only 2 drops of acetic anhydride gave none of the chlorocinnoline.

Chlorination of 6-Chloro-4-hydroxycinnoline.—The cinnoline (0·5 g.), acetic acid (20 c.c.), acetic anhydride (1 c.c.), and sulphuryl chloride (0·42 g.) were refluxed together for 4 hours and worked up as above. The product (0·19 g., 32%), m. p. 301—303°, and its acetyl derivative, m. p. 148—149°, were identical with 3 : 6-dichloro-4-hydroxycinnoline (m. p. 302—303°) and 3 : 6-dichloro-4-acetoxycinnoline (m. p. 149—150°), respectively.

Chlorination of 6-Bromo-4-hydroxycinnoline.—By the same method 6-bromo-4-hydroxycinnoline (0·5 g.) gave 22% of 3-chloro-6-bromo-4-hydroxycinnoline, m. p. 306—307°, giving no depression on admixture with a pure specimen, m. p. 309—310°.

Bromination of 4-Hydroxycinnoline.—4-Hydroxycinnoline (1 g.), acetic acid (20 c.c.), and bromine (1·15 g.) were warmed at 95° for 2½ hours, crystals appearing after ¼ hour. After removal of the solvent under reduced pressure the residue (hydrobromides) was triturated with dilute ammonia solution, leaving a white solid (1·17 g.), m. p. 235—237°. Neutralisation of the ammoniacal washings with acetic acid gave some impure starting material (0·04 g.). Three crystallisations of the product from ethanol gave substantially pure 3-bromo-4-hydroxycinnoline (0·31 g., 20%), m. p. 272—273° showing no depression on admixture with a pure specimen, m. p. 275—276°. The acetyl derivative, m. p. 139—140°, was also identical with 3-bromo-4-acetoxycinnoline, m. p. 139—140°.

Bromination in boiling acetic acid during 1 hour gave 15% of 3-bromo-4-hydroxycinnoline.

Bromination of 6-Chloro-4-hydroxycinnoline.—The cinnoline (1 g.), treated as above, provided after trituration with ammonia a white solid (1·18 g., m. p. 275—276°). Four crystallisations from alcohol gave white needles (0·28 g., 19·5%), m. p. 308—309°, alone and mixed with genuine 6-chloro-3-bromo-4-hydroxycinnoline, m. p. 310—311°. The acetyl derivative, m. p. 165—166°, was identical with 6-chloro-3-bromo-4-acetoxycinnoline, m. p. 166—167°.

Bromination of 6-Bromo-4-hydroxycinnoline.—A white solid (1·02 g.; m. p. 275—277°) was obtained by brominating 6-bromo-4-hydroxycinnoline in the same way as above and triturating the product with ammonia. Four crystallisations from alcohol gave white needles (0·30 g., 22%), m. p. 313—314° (acetyl derivative, m. p. 178—179°), identical with 3 : 6-dibromo-4-hydroxycinnoline, m. p. 315—316° (acetyl derivative, m. p. 179—180°).

Halogenated 4-Hydroxyquinolines.

6-Bromo-4-hydroxyquinoline.—(*a*) *p*-Bromoaniline (25·2 g.) and ethyl ethoxymethylenemalonate (32 g.) (Fuson, Parham, and Reed, *J. Org. Chem.*, 1946, **11**, 194) were heated at 95° for 2 hours, and the alcohol formed was removed under reduced pressure. One crystallisation from methanol gave pale yellow crystals of a product suitable for further use (46 g.; m. p. 98—99°), and further crystallisation gave stout white needles of *ethyl β-(*p*-bromoanilino)-α-carbethoxyacrylate*, m. p. 100—101° (Found: C, 48·4; H, 4·75. C_{1}[illegible]$H_{16}O_4NBr$ requires C, 49·1; H, 4·7%).

(*b*) The above compound (40 g.), finely powdered, was added during 10 minutes to boiling diphenyl ether (400 g.), and the mixture refluxed for ½ hour. After the mixture had cooled, ligroin was added (400 c.c.), and the product collected, washed with more ligroin and some ether, and dried, yielding pure *ethyl* 6-*bromo*-4-*hydroxyquinoline*-3-*carboxylate* (34 g., 99%). It formed lustreless white microcrystals (from alcohol), m. p. 286—287° (Found: C, 48·8; H, 3·5. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4%).

(*c*) The ester (30 g.) was refluxed with potassium hydroxide solution (250 c.c.; 10%) for 2 hours, and the solution filtered (charcoal) and acidified with concentrated hydrochloric acid. The precipitate (22·7 g., 84%) of almost pure 4-*hydroxyquinoline*-3-*carboxylic acid* separated from alcohol in white microcrystals, m. p. 271° (decomp.) (Found: C, 45·5; H, 2·3. $C_{10}H_6O_3NBr$ requires C, 44·8; H, 2·5%).

(*d*) The acid (5 g.) was added to boiling diphenyl ether (25 g.) during 5 minutes, the mixture was boiled under reflux for 25 minutes, cooled, and diluted with ligroin (25 c.c.), and the precipitate collected and washed with ligroin and ether. The substantially pure product (4·02 g.) formed stout pale yellow needles of 6-*bromo*-4-*hydroxyquinoline*, m. p. 282—283°, from alcohol (Found: C, 46·3; H, 3·0. $C_9H_6ONBr,\frac{1}{2}H_2O$ requires C, 46·4; H, 3·0%).

A similar result was obtained by heating the acid at 285° for ½ hour, but the initial product was not so pure as that obtained by the first method.

Chlorination of 4-*Hydroxyquinoline.*—4-Hydroxyquinoline (1 g.) in acetic acid (3·2 c.c.) and acetic anhydride (0·8 c.c.) at 45° was added to sulphuryl chloride (1·05 g.). The mixture was kept at the same temperature for 25 minutes, boiled for 5 minutes, and diluted with water (6 c.c.). The white solid (0·57 g.; m. p. 270—280°) was digested with alcohol (40 c.c.), and the residue (0·24 g.; m. p. >300°) crystallised from alcohol, giving white lustreless microcrystals of a *compound*, m. p. >320° (Found: C, 42·1; H, 2·2. $C_9H_4ONCl_3$ requires C, 43·5; H, 1·6%).

3 : 6-*Dichloro*-4-*hydroxyquinoline.*—6-Chloro-4-hydroxyquinoline (1·64 g.) in acetic acid (9 c.c.) and acetic anhydride (1 c.c.) was added to sulphuryl chloride (1·37 g.) at 45°. There was an immediate reaction and the temperature rose to >100°. The mixture was kept at 60—65° for ½ hour, boiled for 5 minutes, and then cooled, and sodium hydroxide (0·4 g.) in water (6 c.c.) added. Recrystallisation of the almost pure product (1·38 g.) from acetic acid gave lustreless yellow microcrystals of 3 : 6-*dichloro*-4-*hydroxyquinoline*, m. p. >320° (Found: C, 50·6; H, 2·5. $C_9H_5ONCl_2$ requires C, 50·5; H, 2·4%).

3-*Chloro*-6-*bromo*-4-*hydroxyquinoline.*—6-Bromo-4-hydroxyquinoline (1·3 g.) was chlorinated as above, but after addition to sulphuryl chloride (0·87 g.) the mixture was kept at 100° for ½ hour. The product (1·14 g.) formed white microcrystals of 3-*chloro*-6-*bromo*-4-*hydroxyquinoline*, m. p. >320°, from acetic acid (Found: C, 41·8; H, 2·3. $C_9H_5ONClBr$ requires C, 41·8; H, 1·95%).

3-*Bromo*-4-*hydroxyquinoline.*—Addition of bromine (0·72 c.c.) to 4-hydroxyquinoline (2 g.) in acetic acid (6 c.c.) at 70° caused an immediate reaction, the temperature rising to >100°. After 10 minutes at 70° the solution was cooled, and sodium hydroxide (0·55 g.) in water (10 c.c.) added, yielding a white solid (3·03 g.; m. p. 272—274°). Crystallisation from alcohol gave white microcrystals of 3-bromo-4-hydroxyquinoline (2·43 g., 79%), m. p. 281—282° (Riegel *et al.*, *loc. cit.*, give m. p. 288—289°, yield 89%).

6-*Chloro*-3-*bromo*-4-*hydroxyquinoline.*—The quinoline (2 g.), acetic acid (6 c.c.), and bromine (0·6 c.c.) were heated at 95° for 10 minutes, much solid being quickly deposited. Worked up as above, the mixture gave a white solid (2·4 g.) which separated from acetic acid as dull buff microcrystals of 6-*chloro*-3-*bromo*-4-*hydroxyquinoline*, m. p. >320° (Found: C, 42·4; H, 2·2. $C_9H_5ONClBr$ requires C, 41·8; H, 1·95%).

3 : 6-*Dibromo*-4-*hydroxyquinoline.*—6-Bromo-4-hydroxyquinoline (2 g.), treated as above (0·5 c.c. of bromine), gave a pale yellow solid (2·51 g.) which separated from acetic acid as pale yellow microcrystals of 3 : 6-*dibromo*-4-*hydroxyquinoline*, m. p. >320° (Found: C, 35·9; H, 1·7. $C_9H_5ONBr_2$ requires C, 35·7; H, 1·7%).

Halogen Exchange Reactions and Related Experiments with Cinnoline Derivatives.

3 : 4-*Dichloro- and* 3 : 4 : 6-*Trichloro-cinnoline.*—By the usual method (Keneford and Simpson, *loc. cit.*), 3-chloro- (1 g.) and 3 : 6-dichloro-4-hydroxycinnoline (0·4 g.) gave the desired products (0·7 g. and 0·3 g., respectively). 3 : 4-*Dichlorocinnoline* formed white needles, m. p. 126—127°, from ether–ligroin (b. p. 60—80°) (Found: N, 14·8; Cl, 36·2. $C_8H_4N_2Cl_2$ requires N, 14·1; Cl, 35·6%), and 3 : 4 : 6-*trichlorocinnoline* gave pale yellow needles, m. p. 141—142°, from the same solvent (Found: C, 41·2; H, 1·2; Cl, 45·9. $C_8H_3N_2Cl_3$ requires C, 41·15; H, 1·3; Cl, 45·6%).

3-*Chloro*-4-*phenoxycinnoline.*—3 : 4-Dichlorocinnoline (1·5 g.) was converted by standard means (Keneford and Simpson, *loc. cit.*) into 3-*chloro*-4-*phenoxycinnoline* (1·74 g.), which formed white needles, m. p. 120—121°, from ether–ligroin (b. p. 60—80°) (Found: C, 64·7; H, 3·9; N, 10·9. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9%).

Action of Mixed Phosphorus Chlorides on Bromo-4-*hydroxycinnolines.*—The experiments with 3-bromo-4-hydroxycinnoline are described in some detail and serve as a model for those with other compounds, indicating the sort of yield obtained in these reactions. The products from 3-bromo-4-hydroxycinnoline are described in Table II (A), and those obtained under similar conditions from 6-bromo-, 6-chloro-3-bromo-, and 3 : 6-dibromo-4-hydroxycinnoline, in Table II (B), (C), and (D), respectively. All the products were purified by crystallisation from ether–ligroin (b. p. 60—80°).

(i) 3-Bromo-4-hydroxycinnoline (0·5 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (5 c.c.) were heated at 95° for 2 hours in a short-necked flask fitted with a calcium chloride tube, and the mixture was decomposed with ice, basified (20% sodium hydroxide), and extracted with ether. The dried (Na_2SO_4) extract yielded a white solid (0·46 g.).

(ii) The cinnoline (0·4 g.) was treated in the same way, except that the flask was fitted with a water condenser. Yield: 0·38 g.

(iii) The cinnoline (0·4 g.) was treated as in (i), but at 135—140° for 2 hours, the flask being fitted with a short condenser so arranged that the refluxing vapours could just escape, the loss being made up by addition of phosphorus oxychloride from a tap funnel. Yield: 0·39 g.

(iv) The cinnoline (0·4 g.) was treated as in (iii), but under complete reflux. Yield: 0·38 g.

(v) 3-Bromo-4-hydroxycinnoline (0·2 g.) was treated as in (i), but for 24 hours. Yield: 0·19 g.

(vi) The hydroxycinnoline (0·2 g.) was treated as in (iv), but for 24 hours. Yield: 0·18 g.

TABLE II.

Product.				Possible product.			
		Analysis, %.				Analysis, %.	
Conditions.	M. p.[b]	C.	H.	Compound.	M. p.	C.	H.
				(A)			
(i)[a]	146·5—147°	42·1	1·9	3 : 4-Dichlorocinnoline	126—127°	48·3	2·0
(ii)[a]	143—143·5	42·3	2·0				
(iii)[a]	148·5—149·5	39·95	1·75				
(iv)[a,c]	152·5—153	39·9	1·8	4-Chloro-3-bromocinnoline	?	39·5	1·7
(v)[a]	130—131	—	—				
(vi)[a]	143—144	—	—				
				(B)			
(i)[a]	112—113	—	—	4 : 6-Dichlorocinnoline ,	113—114[d]	—	—
(iv)[a]	112—113	—	—				
(i) For ¼ hour	126—127	—	—	4-Chloro-6-bromocinnoline	126—127[d]	—	—
(iv) For ¼ hour[a]	112—113	—	—				
				(C)			
(i) For 1 hour	142—142·5	41·7	1·85	3 : 4 : 6-Trichlorocinnoline	141—142	41·1	1·3
(ii) For 1 hour[a,c]	143—143·5	39·9	1·4				
(iii)[a]	149—149·5	37·6	1·7				
(iv)[a,c]	154—154·5	35·4	1·4	4 : 6-Dichloro-3-bromocinnoline	?	34·6	1·1
(vi)[a]	147—148	—	—				
				(D)			
(i)[a,c]	145·5—146	34·2	1·4	3 : 4 : 6-Trichlorocinnoline	141—142	41·4	1·3
(ii)[a]	146·5—147	34·2	1·4	4 : 6-Dichloro-3-bromocinnoline	?	34·6	1·1
iii)[a]	156—156·5	32·6	1·7				
iv)[a,c]	160·5—161	30·5	1·4	3 : 4-Dichloro-6-bromocinnoline	?	34·6	1·1
(vi)[a]	151—152	—	—	4-Chloro-3 : 6-dibromocinnoline	?	29·8	0·9

(*a*) Bromine was visible in the reaction vessel. (*b*) M. p.s are uncorrected. They were determined with an ordinary thermometer in a small oil-bath, the temperature being raised 1° per minute. Usually 3 specimens were examined at once. Mixtures of the products did not show depressions, but melted at an intermediate temperature. (*c*) These products were phenoxylated. See Table III. (*d*) Leonard and Boyd (*loc. cit.*) give m. p. 113—114° and 126—127°, respectively.

Phenoxylation of Products from Exchange Reactions.—The product (1 part) was heated with phenol (10 parts) at 180° for 2 hours, and the mixture cooled somewhat and poured into excess 5N-sodium hydroxide solution. Ether removed the derivative, which was isolated from the dried (Na_2SO_4) extract in an almost pure state (90—95% yield), and recrystallised from ether–ligroin (b. p. 60—80°), forming white or cream-coloured needles.

Action of Phosphorus Oxychloride on Bromo-4-hydroxycinnolines.—In each case the cinnoline (0·1 g.) and phosphorus oxychloride (2 c.c.) were heated at 95°, or at 135° under reflux, for 2 hours, and the products isolated and crystallised in the usual way. In conjunction with the above results the m. p.s of the products (see Table IV) serve to indicate the extent of halogen exchange.

Action of Phosphorus Pentachloride on Bromo-4-hydroxycinnolines.—An intimate mixture of the cinnoline (0·1 g.) and phosphorus pentachloride (1 g.) was heated, for either 1 hour at 95° or ½ hour at 140—150°, and worked up as before. The results are given in Table V.

Preparation of 4-Chlorocinnolines with Phosphorus Oxychloride.—The hydroxy-compound was refluxed with the oxychloride at 135—140° until a clear solution was obtained, and heating was then continued at 95° to a total of 10 minutes. The products (see Table VI) were isolated as before and crystallised once.

TABLE III.

Supposed 4-chloro-compound.		Product.			Possible product.		
			Analysis, %.			Analysis, %.	
Table II.	Compound.[a]	M. p.	C.	H.	Compound.	C.	H.
A (iv)	4-Chloro-3-bromocinnoline	143—144°	56·15	3·05	3-Bromo-4-phenoxycinnoline	55·8	3·0
C (ii)	3 : 4 : 6-Trichlorocinnoline	107—108	56·7	2·95	3 : 6-Dichloro-4-phenoxycinnoline	57·8	2·8
C (iv)	4 : 6-Dichloro-3-bromocinnoline	113—114	53·2	2·6	6-Chloro-3-bromo-4-phenoxycinnoline	50·1	2·4
D (i)	3 : 4-Dichloro-6-bromocinnoline	128—129	50·1	2·5	3-Chloro-6-bromo-4-phenoxycinnoline	50·1	2·4
D (iv)	4-Chloro-3 : 6-dibromocinnoline	135—136	46·7	2·5	3 : 6-Dibromo-4-phenoxycinnoline	44·1	2·1

(*a*) *I.e.*, the substance to which the analysis in Table II approximates most closely.

TABLE IV.

Compound.	Temp.	Crude product. Yield (g.).	Crude product. M. p.	Recrystallised product. Yield (g.).	Recrystallised product. M. p.
3-Bromo-4-hydroxycinnoline	95°	0·08	136—138°	0·05	141—142°
	135	0·10	151—152	0·08	151—151·5
6-Bromo-4-hydroxycinnoline	95	0·09	116—117	0·04	117—118
	135	0·08	105—107	0·02	112—113
6-Chloro-3-bromo-4-hydroxycinnoline	95	0·09	143—145	0·05	144—145
	135	0·10	151—152	0·07	152—153
3 : 6-Dibromo-4-hydroxycinnoline[a]	95	0·05	141—143	0·04	147—148
	135	0·05	155—156	0·04	158—159

(*a*) 0·05 G. of hydroxy-compound used.

TABLE V.

Compound.	Temp.	Crude product. Yield (g.).	Crude product. M. p.	Crystallised product. Yield (g.).	Crystallised product. M. p.
3-Bromo-4-hydroxycinnoline	95°	0·10	121—123°	0·03	126—127°
	140	0·02	125—130	—	—
6-Bromo-4-hydroxycinnoline	95	0·05	123—125	0·02	125—126
6-Chloro-3-bromo-4-hydroxycinnoline	95	0·10	137—139	0·05	140—141
	140	0·02	132—135	—	—
3 : 6-Dibromo-4-hydroxycinnoline	140	0·04	131—133	0·01	140—141

TABLE VI.

Compound.	Wt., g.	$POCl_3$, c.c.	Time, mins. 140°.	Time, mins. 95°.	Product. G.	Product. M. p.	Recrystallised, m. p.
4-Hydroxycinnoline	0·2	0·6	½	9½	0·17	73—74°	76—77°
3-Chloro-4-hydroxycinnoline	0·1	0·6	2	8	0·1	127—128	127—128
6-Chloro-4-hydroxycinnoline	0·2	0·6	½	9½	0·2	111—112	111—112
3-Bromo-4-hydroxycinnoline	0·1	0·6	2	8	0·1	144—145	149—150
6-Bromo-4-hydroxycinnoline	0·2	0·6	½	9½	0·2	117—118	126—127
6-Chloro-3-bromo-4-hydroxycinnoline	0·1	0·9	4½	5½	0·1	151—152	153—154
3 : 6-Dibromo-5-hydroxycinnoline	0·1	0·9	5	5	0·1	154—155	159—160

TABLE VII.

Compound.[a]	M. p.	Temp.	Product. M. p.	Product. Recrystallised, m. p.
4-Chloro-3-bromocinnoline	151—152°	95°	135—137°	137—138°
		135	138—139	143—144
4 : 6-Dichloro-3-bromocinnoline	153—154	95	140—143	144—145
4-Chloro-3 : 6-dibromocinnoline	160—161	95	144—145	146—147

(*a*) Named according to probable major component, as revealed in above work.

TABLE VIII.

Compound.	Wt., g.	Time, mins. 135°.	Time, mins. 95°.	Product. Wt., g.	Product. M. p.	Product. Recryst., m. p.
6-Chloro-4-hydroxyquinoline	0·5	10	—	0·43	100—101°	103—104°[a]
6-Bromo-4-hydroxyquinoline	0·2	10	—	0·2	108—109	109—110[g]
3-Bromo-4-hydroxyquinoline	0·5	10	—	0·49	68—69	—[b]
3 : 6-Dichloro-4-hydroxyquinoline	0·2	3	7	0·20	103—104	108—109[c]
3-Chloro-6-bromo-4-hydroxyquinoline	0·2	3	7	0·21	127—128	130·5—131[d]
6-Chloro-3-bromo-4-hydroxyquinoline	0·2	2	8	0·21	121—122	124—124·5[e]
3 : 6-Dibromo-4-hydroxyquinoline	0·2	4	6	0·2	130—131	130·5—131·5[g]
3 : 3 : 6-Trichloro-3 : 4-dihydro-4-quinolone (?)	0·1	3	7	0·12	91—93	104—105[f]

(*a*) Riegel *et al.* (*loc. cit.*) give m. p. 105°. (*b*) Riegel *et al.* (*loc. cit.*) give m. p. 67—69°. (*c*) 3 : 4 : 6-*Trichloroquinoline*, m. p. 109·5—110° (Found: C, 46·8; H, 2·0. $C_9H_4NCl_3$ requires C, 46·5; H, 1·7%). (*d*) 3 : 4-*Dichloro-6-bromoquinoline* formed white needles (Found: C, 39·3; H, 1·6. $C_9H_4NCl_2Br$ requires C, 39·1; H, 1·5%). (*e*) 4 : 6-*Dichloro-3-bromoquinoline* gave white needles (Found: C, 39·5; H, 1·55%). (*f*) The product on recrystallisation gave only 13% yields of a specimen which did not depress the m. p. of 3 : 4 : 6-trichlorocinnoline. When pure it gave white needles, m. p. 105—105·5° (Found: C, 47·0; H, 1·9%). (*g*) See following table for analyses.

Action of Mixed Phosphorus Chlorides on Bromo-4-chlorocinnolines.—The 4-chlorocinnolines (1 part), prepared as in the foregoing table, phosphorus pentachloride (2 parts), and phosphorus oxychloride (10 volumes) were heated at 95°, or 135—140° under reflux, and worked up as in previous cases. The results are given in Table VII.

Halogen Exchange Reactions and Related Experiments in the Quinoline Series. Preparation of 4-Chloroquinolines.—The 4-hydroxyquinoline (1 part) and phosphorus oxychloride (3 volumes) were boiled under reflux until a clear solution resulted, and then heated at 95° to make a total heating time of 10 minutes. The products were worked up as described for the cinnoline analogues. The results are given in Table VIII.

Action of Mixed Phosphorus Chlorides on Bromo-4-hydroxyquinolines.—The hydroxy-compound (1 part), phosphorus pentachloride (2 parts), and phosphorus oxychloride (10 volumes) were heated at 95°, or 135—140°, for various times, and worked up as with the cinnoline analogues. The results are recorded in Table IX.

TABLE IX.

Compound.	Wt., g.	Conditions.	Product. Wt., g.	M. p.	Recryst., m. p.
3-Bromo-4-hydroxyquinoline	0·5	95°; 2 hours	0·47	65—66°	67—68°
	0·5	135—140°; 2 hours [a]	0·51	64—65	68—69
	0·5	135—140°; 8 hours [a]	0·38	67—68	69—70 [b]
6-Bromo-4-hydroxyquinoline	0·5	95°; 2 hours	0·49	109—110	109—110 [c]
	0·5	135—140°; 2 hours	0·49	106—108	111—112
6-Chloro-3-bromo-4-hydroxyquinoline	0·2	95°; 2 hours	0·19	121—122	122—122·5
	0·2	135—140°; 2 hours [a]	0·19	119—120	122—123 [d]
	0·2	135—140°; 6 hours [a]	0·19	120—121	122—123
	0·2	135—140°; 24 hours [a]	0·16	120—121	123—124
3 : 6-Dibromo-4-hydroxyquinoline ...	0·5	95°; 2 hours [a]	0·39	131—132	131—132
	0·5	135—140°; 2 hours [a]	0·41	130—131	130—131
	0·5	135—140°; 8 hours [a]	0·39	128—129	130—131 [e]
	0·5	135—140°; 24 hours [a]	0·10	119—120	131—132

(*a*) Bromine visible in reaction vessel. (*b*) This, when pure, formed spiky white needles, m. p. 69—69·5° (Found: C, 45·2; H, 2·15. C_9H_5NClBr requires C, 44·6; H, 2·1%). (*c*) When pure, this gave large white needles, m. p. 110—110·5° (Found: C, 44·6; H, 2·2%). (*d*) As (*c*), m. p. 122—122·5° (Found: C, 40·6; H, 1·5. $C_9H_4NCl_2Br$ requires C, 39·1; H, 1·5%). (*e*) As (*c*), m. p. 130·5—131° (Found: C, 34·6; H, 1·3. $C_9H_4NClBr_2$ requires C, 33·6; H, 1·25%).

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UNIVERSITY COLLEGE OF THE SOUTH WEST, EXETER.

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86. *Cinnolines. Part XXVI. Some 4-Cinnolylhydrazines, Their Preparation and Oxidation. Miscellaneous Quinoline Derivatives.*

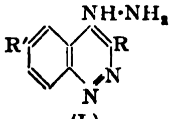
By K. SCHOFIELD and T. SWAIN.

4-Cinnolylhydrazine and its *3-chloro-*, *6-chloro-*, and *6-bromo-*derivatives are described. Except for the 3-chloro-compound, these are oxidised by aqueous copper sulphate to the corresponding *cinnolines*. *4-Phenylhydrazino-* and *3-chloro-4-phenylhydrazino-cinnoline* have been prepared. Attempts to prepare derivatives of 3-aminocinnoline are mentioned, and miscellaneous quinoline derivatives reported.

FROM the reaction between hydrazine and 4-chloroquinaldine Backeberg and Friedmann (*J.*, 1938, 972) obtained either of two products, according to the conditions. Condensation in hot alcohol gave 4-quinaldylhydrazine, whilst reaction at a higher temperature, under pressure, gave an isomeric compound which the authors suggested to be 3 : 4-diaminoquinaldine. Various pieces of evidence made this structure uncertain, but only after this work had begun was it completely disproved (Koenigs and Freund, *Ber.*, 1947, **80**, 143).

Since we desired to prepare 3 : 4-diaminocinnolines, in the light of Backeberg and Friedmann's suggestion it seemed of interest to examine the reaction between 4-chlorocinnolines and hydrazine. Further, 4-cinnolylhydrazines offered the possibility of obtaining, by oxidation, hitherto unknown derivatives of cinnoline unsubstituted at $C_{(4)}$.

4-Chlorocinnoline reacted with hydrazine in alcohol much more slowly and less vigorously than did 4-chloroquinazoline (Dewar, *J.*, 1944, 619; we have repeated the reaction for comparative purposes). Though only qualitative, the observation is in agreement with the calculations of Longuet-Higgins and Coulson (*J.*, 1949, 971), which indicate that $C_{(4)}$ in quinazoline should be more susceptible to nucleophilic attack than the same position in cinnoline. The product of the reaction was a deep orange-coloured solid, m. p. 293—294° (decomp.), but after two crystallsations from alcohol its m. p. changed to 226—227° (decomp.). The high-melting form was produced in a reaction carried out under pressure. In view of the behaviour of 4-chloroquinaldine, it was at first thought that isomerisation was involved, but experiment showed that the substances were merely different crystalline forms of 4-*cinnolylhydrazine* (I; R = R′ = H). Thus, both gave the same *hydrochloride*, and the same *diacetyl* derivative. Any possibility that the low-melting form might be 3 : 4-diaminocinnoline was removed by the formation from it of a *monoformyl* derivative, and of a *product* $C_{22}H_{14}ON_4$ (II) with phenanthraquinone. Finally, both substances gave cinnoline when oxidised with aqueous copper sulphate.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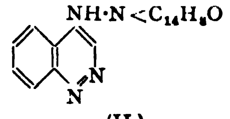
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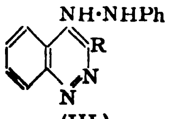
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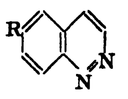
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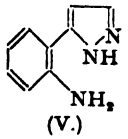
(V.)

3-*Chloro-* (I; R = Cl, R′ = H), 6-*chloro-* (I; R = H, R′ = Cl), and 6-*bromo-4-cinnolylhydrazine* (I; R = H, R′ = Br) were prepared in the same way, but none of these showed polymorphism. Replacement of hydrazine by phenylhydrazine in the reaction gave 4-*phenylhydrazino-* (III; R = H), and 3-*chloro-4-phenylhydrazino-cinnoline* (III; R = Cl).

On oxidation with aqueous copper sulphate 3-chloro-4-cinnolylhydrazine underwent violent decomposition and no recognisable product was isolated. In contrast 6-chloro- and 6-bromo-4-cinnolylhydrazine readily gave 6-*chloro-* (IV; R = Cl), and 6-*bromo-cinnoline* (IV; R = Br). Dewar (*loc. cit.*) reported that 4-quinazolylhydrazine was unaffected by acid or neutral copper sulphate, but was oxidised by Fehling's solution, some quinazoline being formed. In our hands, aqueous copper sulphate oxidised 4-quinazolylhydrazine to an unidentified product, the *picrate* of which gave analyses in rough agreement with those required for a hydroxyquinazoline derivative, but which appears to differ from 4-hydroxyquinazoline picrate (Bogert and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031).

A few attempts to introduce an amino-group by replacement of halogen in 3-halogenocinnolines failed. 3-Bromo-4-hydroxycinnoline gave no recognisable product when heated with aqueous ammonia in the presence of copper sulphate. 3-Bromo-4-hydroxycinnoline was the only isolable product from the reaction between 4-chloro-3-bromocinnoline and alcoholic ammonia under pressure, but in similar circumstances 3 : 4-dichlorocinnoline gave 3-*chloro-4-aminocinnoline*, identical with a specimen prepared from 3-chloro-4-phenoxycinnoline. The use of aqueous ammonia in this case gave a mixture of the 4-amino-compound and 3-chloro-4-hydroxycinnoline. With either aqueous or alcoholic ammonia 4 : 6-dichlorocinnoline gave only 6-chloro-4-hydroxycinnoline. The erratic nature of these results, and the experience of Keneford, Schofield, and Simpson (*J.*, 1948, 358) and of Baker (*J.*, 1948, 1713) with reactions of this type, suggest that they would merit closer examination.

Backeberg and Friedmann (*loc. cit.*), by treating 4-chloroquinoline with hydrazine under pressure, obtained a product, m. p. 129°, which they supposed to be 3 : 4-diaminoquinoline, but which, in view of the work of Koenigs and Freund (*loc. cit.*), must now be regarded as (V). Approaching the problem before the results of Koenigs and Freund appeared, we found it necessary first to compare Backeberg and Friedmann's product directly with authentic specimens of 4-quinolylhydrazine and 3 : 4-diaminoquinoline, which they had not done. 4-Quinolylhydrazine was described by Brydowna (*Rocz. Chem.*, 1932, **12**, 88; only an abstract was available to us), but in trying to repeat the preparation, whilst 4-*quinolylhydrazine hydrochloride* was readily obtained, attempts to form the free base gave a white solid, m. p. 135—140° (Brydowna, *loc. cit.*, gives m. p. 140—142°), which rapidly decomposed in air (Knueppel, *Annalen*, 1900, **310**, 82, reported that 6-quinolylhydrazine is likewise unstable). 3 : 4-Diaminoquinoline was obtained by Renshaw, Friedman, and Gajewski (*J. Amer. Chem. Soc.*, 1939, **61**, 3322) by reducing 3-amino-4-phenylazoquinoline, and by the action of ammonia on 3-bromo-4-aminoquinoline. We have now prepared it from 3-nitro-4-aminoquinoline, and characterised it as its *hydrochloride* and *diacetyl* derivative.

EXPERIMENTAL.

(M. p.s are uncorrected.)

4-*Cinnolylhydrazine.*—(*a*) (i) 4-Chlorocinnoline (2 g.) and hydrazine (2 c.c.; 90%) in alcohol (50 c.c.) were left for 4 days at room temperature. (Under similar conditions 4-chloroquinazoline reacted immediately, with evolution of heat and precipitation of the product.) The mixture of yellow crusts and hydrazine hydrochloride formed was collected and washed with water, giving a deep orange crystalline solid (1·77 g., 91%), m. p. 293—294° (decomp.) (the substance turned deep red at 200—210°). The use of 50% hydrazine hydrate gave slightly lower yields (81%).

(ii) 4-Chlorocinnoline (0·76 g.) and hydrazine hydrate (1·5 c.c.; 90%) were heated for 22 hours at 150—160° in a sealed tube. The product (0·70 g.; m. p. 150—160°) on crystallisation from alcohol gave deep-red leaflets (0·22 g.), m. p. 290—291° (decomp.) (changing colour as before), which did not depress the m. p. of the product from (i).

(*b*) One crystallisation from alcohol of the product from (i) gave bright orange plates, m. p. 296—297°; a second crystallisation from the same solvent gave orange plates, m. p. 224—226° (decomp.) (becoming deep red at 180°). Further crystallisation gave 4-*cinnolylhydrazine*, m. p. 226—227° (decomp.) (Found: C, 59·7; H, 5·1; N, 34·7. $C_8H_8N_4$ requires C, 59·9; H, 5·0; N, 34·9%). Either the high- or the low-melting form of the compound dissolved in hot concentrated hydrochloric acid to give very small white crystals of a hydrochloride, m. p. 244—245° (not analysed). Either form when treated with boiling acetic anhydride gave the *diacetyl* derivative, which formed white crystals, m. p. 208—209°, from alcohol (Found: C, 58·6; H, 4·9. $C_{12}H_{12}O_2N_4$ requires C, 58·9; H, 4·9%). Hot anhydrous formic acid likewise gave the *monoformyl* derivative, which formed yellow plates, m. p. 229—230°, from hot water (Found: C, 57·4; H, 4·6. $C_9H_8ON_4$ requires C, 57·4; H, 4·3%). When treated with phenanthraquinone in boiling acetic anhydride, 4-cinnolylhydrazine gave a *monohydrazono*-derivative, which formed glistening red microcrystals, m. p. 267—268°, from alcohol (Found: C, 74·6; H, 4·3; N, 15·0. $C_{22}H_{14}ON_4$ requires C, 75·4; H, 4·0; N, 15·9%).

3-*Chloro*-4-*cinnolylhydrazine.*—As in the above case, 3 : 4-dichlorocinnoline (1·26 g.) and hydrazine (1·5 c.c.; 90%), in alcohol (20 c.c.), gave a product [1·10 g.; m. p. 255° (decomp.)] which formed orange leaflets of 3-*chloro*-4-*cinnolylhydrazine*, m. p. >300° (becoming deep red at 200—220°) (Found: C, 49·4; H, 3·7. $C_8H_7N_4Cl$ requires C, 49·4; H, 3·6%).

6-*Chloro*-4-*cinnolylhydrazine.*—In the same way, from 4 : 6-dichlorocinnoline (1·85 g.), hydrazine hydrate (2 c.c.), and alcohol (120 c.c.), a product was obtained (0·65 g.; m. p. >320°) which formed orange yellow crystals of 6-*chloro*-4-*cinnolylhydrazine*, m. p. >320° (turning deep red at 220°), from alcohol (Found: C, 49·1; H, 3·7%).

6-*Bromo*-4-*cinnolylhydrazine.*—4-Chloro-6-bromocinnoline (2·25 g.) likewise gave a product (1·93 g.; m. p. >300°), which was digested with alcohol and reprecipitated from hydrochloric acid solution with ammonia, forming orange microcrystals of 6-*bromo*-4-*cinnolylhydrazine*, m. p. >300° (becoming deep red at 220°) (Found: C, 41·1; H, 3·3. $C_8H_7N_4Br$ requires C, 40·2; H, 2·9%).

Oxidation of 4-*Cinnolylhydrazines.*—(i) 4-Cinnolylhydrazine (0·2 g.) was heated under reflux with water (2 c.c.), a solution of copper sulphate (4 c.c.; 10%) was added dropwise during 5 minutes (a vigorous reaction ensued), and the mixture was then boiled for ½ hour. Filtration, basification of the filtrate, and ether-extraction removed an oil (0·09 g.). Dissolved in ether (5 c.c.) and treated with picric acid [0·20 g., in benzene (2 c.c.)], this gave a precipitate which formed khaki leaflets, m. p. 191·5—192·5°, from alcohol (Found: C, 47·2; H, 3·7. Calc. for $C_{14}H_9O_7N_5$: C, 46·8; H, 2·5%), identical with cinnoline picrate (Busch and Rast, *Ber.*, 1897, **30**, 521).

(ii) 6-Chloro-4-cinnolylhydrazine (0·5 g.) under the same conditions reacted with moderate vigour and yielded a buff-coloured solid, crystallising from ether-ligroin (b. p. 60—80°) as pale brown lustreless prisms of 6-*chlorocinnoline* (0·14 g.), m. p. 119—120° (Found: C, 58·8; H, 3·5. $C_8H_5N_2Cl$ requires C, 58·4; H, 3·1%).

(iii) 6-Bromo-4-cinnolylhydrazine (2 g.) likewise gave 6-*bromocinnoline* (0·47 g.), which formed pale buff-coloured needles from ether–ligroin (b. p. 60—80°), m. p. 129—130° (Found: C, 46·9; H, 2·8. $C_8H_5N_2Br$ requires C, 46·0; H, 3·2%).

(iv) Under these conditions 3-chloro-4-cinnolylhydrazine underwent violent oxidation, and the tarry product could neither be crystallised nor converted into a picrate.

Oxidation of 4-*Quinazolylhydrazine.*—4-Quinazolylhydrazine (0·2 g.), oxidised as above, gave an oily solid which, treated with picric acid (0·1 g.), in alcohol (4 c.c.), gave a *picrate* (0·14 g.), forming yellow microcrystals, m. p. 151—152°, from alcohol (Found: C, 45·4; H, 2·5; N, 16·4. $C_{14}H_9O_8N_5$ requires C, 44·8; H, 2·4; N, 18·6%) (Bogert and Hand, *loc. cit.*, give m. p. 204—205° for 4-hydroxyquinazoline picrate).

4-*Phenylhydrazinocinnoline.*—A solution of 4-chlorocinnoline (1·9 g.), alcohol (45 c.c.), and phenylhydrazine (3 g.) was left for 3 days at room temperature, filtered from phenylhydrazine hydrochloride, the alcohol removed *in vacuo*, and the tarry residue washed with water and dried on a porous plate. After repeated extraction with ether and crystallisation from alcohol, the solid gave yellow rhombs of 4-*phenylhydrazinocinnoline* (0·52 g.), m. p. 238° (decomp.) (Found: 64·1; H, 5·0. $C_{14}H_{12}N_4,1\frac{1}{2}H_2O$ requires C, 63·9; H, 5·5%).

3-*Chloro*-4-*phenylhydrazinocinnoline.*—3 : 4-Dichlorocinnoline (0·5 g.) and phenylhydrazine (0·75 g.), in alcohol (20 c.c.), were left for 6 days at room temperature, and then worked up as above. Crystallisation of the crude product from dilute alcohol gave lustreless brown leaflets (0·39 g.) of 3-*chloro*-4-*phenylhydrazinocinnoline*, m. p. 134—135° (Found: C, 62·5; H, 4·4. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1%).

4-*Quinolylhydrazine Hydrochloride.*—4-Chloroquinoline (1 g.), hydrazine hydrate (1 c.c.; 90%), and alcohol (10 c.c.) were heated under reflux for 8 hours in an atmosphere of nitrogen. Removal of the alcohol, extraction with ether, concentration of the extract to *ca.* 20 c.c., and drying (Na_2SO_4), followed by passage of dry hydrogen chloride, gave a granular solid. Recrystallisation from dilute alcohol provided white microcrystals (0·21 g.) of *4-quinolylhydrazine hydrochloride*, m. p. 300—301° (Found : C, 55·1; H, 5·3. $C_9H_9N_3$,HCl requires C, 55·3; H, 5·2%). In other experiments the free base was isolated as a white solid, m. p. 135—140° (Brydowna, *loc. cit.*, gives m. p. 140—142°), which decomposed in a few hours in the air to a black mass with a strong quinoline-like smell.

3 : 4-*Diaminoquinoline*.—(*a*) 3-Nitro-4-aminoquinoline was obtained by a method essentially similar to that since described by Albert *et al.* (*J.*, 1948, 1284), and also from 3-nitro-4-phenoxyquinoline (Schofield and Swain, *J.*, 1949, 1367) as follows. The phenoxy-compound (0·5 g.) was added to ammonium acetate (previously heated at 180°) at 160°, and the temperature raised to 210° during 8 minutes. After 10 minutes at this temperature the mixture was cooled and diluted with water, and the precipitate (0·30 g.) crystallised from alcohol. 3-Nitro-4-aminoquinoline formed yellow needles, m. p. 261—262° (Found : C, 57·2; H, 3·7. Calc. for $C_9H_7O_2N_3$: C, 57·3; H, 3·8%).

(*b*) 3-Nitro-4-aminoquinoline (0·81 g.) in concentrated hydrochloric acid (16 c.c.) was treated with stannous chloride (4 g.) in the same solvent (10 c.c.) at 95°, and the solution heated at this temperature for 2 hours. The mixture was basified with concentrated sodium hydroxide solution, extracted with ether, the extract washed with 6N-sodium hydroxide solution and water, and, after drying (Na_2SO_4), the ether was removed. Crystallisation of the almost pure residue (0·6 g.) from water gave 3 : 4-diaminoquinoline in two forms: one, solvent-free brown prisms, m. p. 171—172° (Found: C, 67·6; H, 5·7. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7%) (Renshaw *et al.*, *loc. cit.*, give m. p. 174°), and the other, lustreless pale brown needles, m. p. 93—94° (Found : C, 63·6; H, 5·6; N, 24·7. $C_9H_9N_3,\frac{1}{2}H_2O$ requires C, 64·3; H, 5·9; N, 24·9%). The diamine, m. p. 171—172°, when treated in ether with dry hydrogen chloride, gave very small white crystals of a hydrochloride, m. p. 298—299° (not analysed). Boiling acetic anhydride converted the diamine into a *diacetyl* derivative, which crystallised from dilute methanol in small white needles, m. p. 230—231° (Found : C, 62·2; H, 6·3. $C_{13}H_{13}O_2N_3,H_2O$ requires C, 62·3; H, 5·6%).

3-*Chloro-4-aminocinnoline*.—(*a*) 3-Chloro-4-phenoxycinnoline (1·5 g.) (see previous paper) was added in one portion to ammonium acetate (9 g.; previously heated to 180°) at 160°. Dilution with water gave a precipitate of 3-chloro-4-hydroxycinnoline (0·19 g.). Basification of the filtrate from this, with ammonia (*d* 0·88), gave a precipitate (0·57 g.) of 3-*chloro-4-aminocinnoline*, which formed fine white needles, m. p. 228—229°, from alcohol (Found : C, 53·2; H, 3·4. $C_8H_6N_3Cl$ requires C, 53·5; H, 3·4%).

(*b*) 3 : 4-Dichlorocinnoline (0·5 g.) in saturated alcoholic ammonia (10 c.c.) was heated for 22 hours at 150—160° in a sealed tube. Removal of the alcohol from the product, and crystallisation from dilute alcohol, gave 3-chloro-4-aminocinnoline (0·33 g.), identical with the above.

3 : 4-Dichlorocinnoline (0·5 g.), treated in the same way with aqueous ammonia (5 c.c.; *d* 0·88), gave 3-chloro-4-aminocinnoline (0·08 g.) and 3-chloro-4-hydroxycinnoline (0·23 g.).

Under the above conditions, with either alcoholic or aqueous ammonia, both 4-chloro-3-bromo- and 4 : 6-dichloro-cinnoline gave only the 4-hydroxy-compounds.

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Washington Singer Laboratories,
University College of the South West, Exeter.

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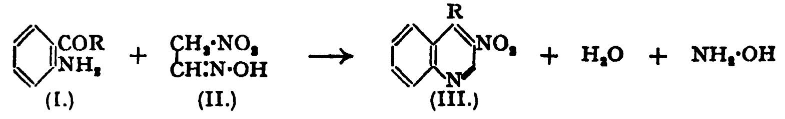
87. *Reactions of Methazonic Acid. Part I. The Preparation of 3-Nitrolepidines and 3-Nitro-4-arylquinolines.*

By K. Schofield and R. S. Theobald.

The course of the reaction between methazonic acid and substituted 2-aminoacetophenones depends on the nature of the substituent. In dilute mineral acid the initial product is a *o*-(2-nitroethylideneamino)acetophenone, or in some cases the oxime of this derivative. *o*-(2-Nitroethylideneamino)acetophenones undergo cyclisation to 3-nitrolepidines and hydrolysis to the parent amines in varying degrees when treated with dilute sodium hydroxide solution. Both they and their oximes are quantitatively cyclised by activated alumina, except in a few special cases. Derivatives of *o*-aminobenzophenone behave similarly, leading finally to 3-nitro-4-arylquinolines. 3-*Nitro*-4-2′-*pyridylquinoline* is described.

3-Nitroquinoline and its derivatives have been little studied, probably on account of their inaccessibility. Few synthetic routes to these compounds are known. Only eight cases of direct nitration at the 3-position have been described, and these concern either hydroxy- or amino-quinolines; they are 4-hydroxyquinaldine (Conrad and Limpach, *Ber.*, 1887, **20**, 950; 1888, **21**, 1981; Kermack and Weatherhead, *J.*, 1939, 563), 2 : 4-dihydroxyquinoline (Gabriel, *Ber.*, 1918, **51**, 1500; Ashley, Perkin, and Robinson, *J.*, 1930, 382), *N*-oxides of 4-hydroxyquinaldine and 4-hydroxy-2-phenylquinoline (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, 1613), 2-hydroxy-4 : 6-dimethylquinoline (Balaban, *J.*, 1930, 2346), 4 : 6-diaminoquinoline and derivatives (F.P. 779,092; G.P. 613,065; U.S.P. 2,066,730), 7-chloro-4-hydroxyquinoline (Breslow *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1232), and 4-hydroxyquinoline (Schofield and Swain, *J.*, 1949, 1367). Again, apart from the possible preparation of 3-nitrocarbostyril (Friedländer and Lazarus, *Annalen*, 1885, **229**, 243; Decker, *J. pr. Chem.*, 1901, **64**, 101) by a method of limited utility, only two synthetic routes to 3-nitroquinolines are available. The more recent of these (Uhle and Jacobs, *J. Org. Chem.*, 1945, **10**, 76; Morley and Simpson, *J.*, 1948, 2024) depends on the reaction of an aromatic amine with nitromalonaldehyde, and is limited to 3-nitroquinolines unsubstituted at $C_{(4)}$. The earlier known synthesis utilises the reaction between methazonic acid (II) and an *o*-aminoarylaldehyde or ketone (I; R = H or alkyl), an isatin derivative (I; R = CO_2H), or an anthranilic acid (I; R = OH) (G.P. 335,197, 347,375; Friedländer, **13**, 818; **14**, 521), in dilute mineral acid solution.

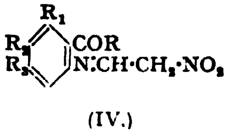


(I.) (II.) (III.)

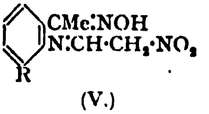
The methazonic acid synthesis has received little attention, except for the preparation of individual compounds, no systematic study having been reported. Bargellini and Settimj (*Gazzetta*, 1923, **53**, 601) repeated the preparation, described in a patent, of 3-nitroquinoline, Renshaw and Friedman (*J. Amer. Chem. Soc.*, 1939, **61**, 3320; cf. Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 709) reported a yield of 22% in the same instance, and Clemo and Swan raised this to 48% by carrying out the reaction in alcohol containing concentrated hydrochloric acid (*J.*, 1945, 867). Clemo and Swan (*loc. cit.*) also reported successful application of the reaction, though with mediocre yields, to 6-aminopiperonal and 6-aminoveratraldehyde, but Ruggli and Frey (*Helv. Chim. Acta*, 1939, **22**, 1413) obtained only a complex product from 4 : 6-diamino*iso*phthalaldehyde. Several workers have prepared 3-nitro-4-hydroxyquinolines from variously substituted anthranilic acids (Colonna, *Gazzetta*, 1937, **67**, 46; 1939, **69**, 684; Musajo, *ibid.*, 1937, **67**, 222; Bachman *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 365; Breslow *et al.*, *loc. cit.*; Albert, Brown, and Duewell, *J.*, 1948, 1284). It is relevant that these reactions with anthranilic acids always proceed through the intermediate formation of a 2-nitroethylideneamino-compound (IV; R = OH), the cyclisation of which (always in mediocre yield) has only been achieved by sodium acetate in acetic anhydride solution. Applications of the reaction involving isatins will be described in a subsequent paper.

With regard to 2-aminoarylaldehydes and ketones, the original patent describes the use of *o*-aminobenzaldehyde and *o*-aminoacetophenone, and a similar reaction procedure was said to be applicable to various unspecified (including halogeno-)2-aminobenzaldehydes, and to aldehydes and ketones of the naphthalene or anthracene series. Although 2-aminobenzaldehydes are difficult to obtain, many 2-aminoacetophenones are now available, and this fact, coupled with our interest in the possible products and substances to be obtained from them, prompted the present investigation of the scope of the reaction between 2-aminoarylketones and methazonic acid, as a source of 3-nitroquinoline derivatives.

Before examining substituted 2-aminoketones we re-investigated the method described in the patent for preparation of 3-nitrolepidine itself, which consists in treating *o*-aminoacetophenone, in dilute hydrochloric acid solution, with aqueous sodium methazonate, and subsequently acidifying the solution with an unspecified quantity of hydrochloric acid. The yellow precipitate formed at room temperature, said to be a mixture of 3-nitrolepidine and *o*-aminoacetophenone oxime, is stated to be readily freed from the latter by dilute sodium hydroxide solution. We noticed, however, that the initial reaction product dissolved completely in cold dilute alkali, and only after some seconds was the quinoline derivative precipitated. Clearly, 3-nitrolepidine could not have been formed in the original condensation, since it is insoluble in alkali, and it therefore seemed likely that the reaction, like that with anthranilic acids, proceeds in two stages. Recrystallisation of the initial condensation product led to the isolation of o-(*2-nitroethylideneamino)acetophenone* (IV; R = Me, $R_1 = R_2 = R_3$ = H). Cyclisation of the pure nitroethylideneamino-compound by cold dilute alkali was quantitative, and its facility is in



(IV.)



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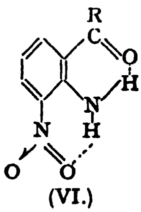


(VI.)

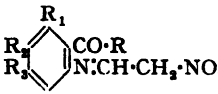
great contrast to the case of the analogous derivatives of anthranilic acids (IV; R = OH), mentioned above. Recovery of 3-nitrolepidine by the method described in the patent never exceeded 14%, based on the amino-ketone. A small improvement (25%) was obtained by careful adjustment of the amount of dilute mineral acid, and by using solid methazonic acid. The obvious discrepancy between the fact that (IV; R = Me, $R_1 = R_2 = R_3$ = H) is quantitatively cyclised to (III; R = Me) by dilute alkali, and the small overall yield of 3-nitrolepidine from the reaction between *o*-aminoacetophenone and methazonic acid under the conditions employed led us to a closer examination of them. This particular reaction has in fact proved to be complex, and further discussion of it is reserved for a later publication.

The more convenient procedure using solid methazonic acid was adopted in all subsequent work with other amino-ketones, and in most cases it also proved necessary to include an organic solvent, usually acetone, in order to ensure homogeneous reaction media. The 4-, 5-, and 6-monosubstituted and 4 : 5-disubstituted 2-aminoacetophenones examined invariably gave compounds of type (IV), always in higher yield than in the case of *o*-aminoacetophenone itself (Table I). Apart from a general tendency for electronegative substituents, particularly *para* to the amino-group, to facilitate the condensation, the results are not entirely clear-cut from the electronic standpoint. One reason for this may lie in the differing solubilities of the products in the varying reaction media, but it may also be that in some cases various side-reactions occur, similar to those shown to a pronounced degree by *o*-aminoacetophenone, though this possibility was not investigated.

Several 3-substituted 2-aminoacetophenones were examined, and in each case the reaction proved in some way unusual. 3-Chloro-, 3-bromo-, and 3-*iodo-2-aminoacetophenone* (see below) each reacted with methazonic acid in acetone–dilute hydrochloric acid to give paler products than the normal condensation derivatives (IV). These gave no reaction for a free amino-group, but appeared to be amphoteric since they did not separate from the acid reaction mixture before dilution (in contrast to IV), and also dissolved easily in dilute alkali without cyclising to a quinoline derivative. At present we regard these substances as the oximes (V; R = Cl, Br, or I) of the related 2-nitroethylideneamino-compounds (Table II). After melting with effervescence, they solidified and remelted at a higher temperature. Although the point was not directly proved, it is probable that the second m. p. is that of the corresponding 3-nitrolepidine (see below), formed by elimination of hydroxylamine. Available knowledge of oxime–ketone hydrolysis equilibria (see, *e.g.*, Conant and Bartlett, *J. Amer. Chem. Soc.*, 1932, **54**, 2881) does not make clear why in these cases oxime formation of the acetophenone should be favoured, in contrast to the apparently similar cases of 5-halogeno-2-aminoacetophenones mentioned above. 2-Amino-3-methylacetophenone with an electron-releasing substituent was expected to provide a useful comparison, but in fact it constituted another variation on the normal course of reaction, since 3-*nitro*-4 : 8-*dimethylquinoline* resulted directly in this case. 3-Nitro-2-aminoacetophenone failed to react with methazonic acid in acetone–hydrochloric acid, either at room temperature or at 95°. In view of the relative steric effectiveness of halogen, methyl, and nitro-groups, *e.g.*, in restricting free rotation in the diphenyl series (Gilman, "Organic Chemistry, An advanced Treatise," 1943, p. 362), this failure is probably not due to steric hindrance, and we attribute it to hydrogen bonding in the structure of 3-nitro-2-aminoacetophenone (VI; R = Me).

The second stage of the synthesis of 3-nitrolepidines, the cyclisation of compounds (IV), showed interesting variations. In effecting this step with dilute alkali, besides cyclisation, hydrolysis to the original amine may occur. The ease of these competing reactions varied considerably. Thus 5-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = R_3$ = H, $R_2 = NO_2$) was converted into 3 : 6-*dinitrolepidine* during attempted crystallisation from aqueous acetone, and 4-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = R_2$ = H, $R_3 = NO_2$) was partly cyclised to 3 : 7-*dinitrolepidine* by hot acetone. However, 4-, 5-, and 6-*nitro*-2-(2-*nitroethylideneamino*)*acetophenone* (IV; R = Me, $R_1 = NO_2$, $R_2 = R_3$ = H) were all completely hydrolysed to the parent amines by dilute alkali. Although this great ease of alkaline hydrolysis was confined to the *Bz*-nitro-compounds, some degree of hydrolysis did occur with most other compounds of type (IV), as manifested in the diminished yields of 3-nitrolepidines (Table III). The results do not at first sight appear to indicate a consistent effect, depending on the electronic character of the substituent, upon the behaviour of these Schiff's bases towards dilute alkali, but it must be remembered that the two competing reactions of alkaline hydrolysis and cyclisation are each affected in a complicated way by the character of substituents. Depending on its position, a substituent may exert its chief effect on the ketone group, increasing or decreasing its electrophilic nature, upon the azomethine linkage, increasing or decreasing its ease of hydrolysis, or upon the nitroethylideneamino-group, augmenting or

TABLE I.



	R.	R$_1$.	R$_2$.	R$_3$.	Yield, %.[1]	M. p. (decomp.).	Form.	Solvent.[2]	Formula.	Analysis, %. Found. C.	H.	Calc. C.	H.
(1)	CH$_3$	H	H	H	27	124—125°	Bright yellow leaflets	b	$C_{10}H_{10}O_3N_2$	58·1	5·2	58·25	4·85
(2)	,,	NO$_2$	H	H	80	187—188	Yellow leaflets	c	$C_{10}H_9O_5N_3$	48·2	3·8	47·8	3·6
(3)	,,	H	NO$_2$	H	85	214—216	Yellow needles	a[3]	,,	47·8	3·6	47·8	3·6
(4)	,,	H	H	NO$_2$	55	207—208	Yellow leaflets	Not recryst.[4]	,,	46·7	3·6	47·8	3·6
(5)	,,	H	Cl	H	75	190—191	Yellow cubes	a	$C_{10}H_9O_3N_2Cl$	49·9	3·7	49·9	3·7
(6)	,,	H	H	Cl	50	199—200	Pale yellow solid	c	,,	50·0	3·6	49·9	3·7
(7)	,,	H	CH$_3$	H	54	192—193	Yellow prisms	a	$C_{11}H_{12}O_3N_2$	60·0	5·8	60·0	5·5
(8)	,,	H	CH$_3$	CH$_3$	49	214—215	Pale yellow solid	a	$C_{12}H_{14}O_3N_2$	62·0	6·7	61·5	6·0
(9)	,,	H	CH$_3$O	CH$_3$O	59	192—193	Orange microneedles	a	$C_{12}H_{14}O_5N_2$	54·3	5·0	54·1	5·3
(10)	,,	H	–[CH$_2$]$_3$–		44	221—222	Yellow needles	a	$C_{13}H_{14}O_3N_2$	63·0	5·7	63·4	5·7
(11)	,,	H	–[CH$_2$]$_4$–		79	212—213	Yellow needles	a	$C_{14}H_{16}O_3N_2$	64·1	6·2	64·6	6·2
(12)	Ph	H	H	H	78	135—136	Yellow needles	b	$C_{15}H_{12}O_3N_2$	66·75	4·3	67·2	4·5
(13)	,,	NO$_2$	H	H	66	163—164	Pale yellow needles	d	$C_{15}H_{11}O_5N_3$	57·6	3·6	57·5	3·5
(14)	,,	H	NO$_2$	H	71	187—188	Yellow needles	a	,,	57·9	3·8	57·5	3·5
(15)	,,	H	H	NO$_2$	65	175—176	Yellow microneedles	a	,,	57·5	3·75	57·5	3·5
(16)	*p*-C$_6$H$_4$·OMe	H	H	H	79	164—165	Pale yellow needles	b	$C_{16}H_{14}O_4N_2$	64·0	5·0	64·4	4·7

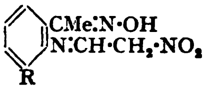
[1] Uncrystallised product—usually substantially pure.

[2] a = Acetone; b = alcohol; c = aqueous acetone; d = acetone–alcohol.

[3] Repeated crystallisation from aqueous acetone caused cyclisation.

[4] Attempted crystallisation from acetone caused cyclisation.

TABLE II.

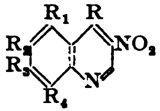


	R.	Yield, %.[1]	M. p.	Form.	Solvent.	Formula.	Analysis, %. Found. C.	H.	N.	Calc. C.	H.	N.
(17)	Cl	46	170° (218—219°)	Pale yellow leaflets	Acetone	$C_{10}H_{10}O_3N_3Cl$	46·5	4·0	16·0	47·0	3·9	16·4
(18)	Br	35	170 (207—208)	Pale yellow cubes	Acetone	$C_{10}H_{10}O_3N_3Br$	39·8	3·5	13·5	40·0	3·4	14·0
(19)	I[2]	38	140 (183—184)	Pale yellow prisms	Acetone	$C_{10}H_{10}O_3N_3I,\frac{1}{2}H_2O$	33·9	2·7	—	33·7	3·1	—

[1] Yield of crude product.

[2] Insufficient of the compound was available for cyclisation.

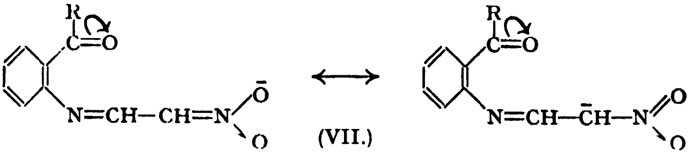
TABLE III.



R.	R_1.	R_2.	R_3.	R_4.	Yield, %.[1] A.	Yield, %.[1] B.	M. p.	Form.	Solvent.[2]	Formula.	Analysis, %. Found. C.	Analysis, %. Found. H.	Analysis, %. Calc. C.	Analysis, %. Calc. H.
CH_3	H	H	H	H	92	Q	117—118°	Colourless needles	a	$C_{10}H_8O_2N$	63·3	3·8	63·8	4·25
"	NO_2	H	H	H	0	75	131—132	Pale pink needles	b	$C_{10}H_7O_4N_3$	50·9	3·2	51·5	3·0
"	H	NO_2	H	H	0	Q	168—169	Pale pink needles	c	$C_{10}H_7O_4N_3$	51·0	3·25	51·5	3·0
"	H	H	NO_2	H	0	Q	182—183	Pale yellow needles	c	$C_{10}H_7O_4N_3$	51·95	3·0	51·5	3·0
"	H	Cl	H	H	86	Q	149—150	Fawn needles	a	$C_{10}H_7O_2N_2Cl$	53·6	3·3	53·9	3·15
"	H	H	Cl	H	60	Q	137—138	Colourless needles	b	$C_{10}H_7O_2N_2Cl$	54·1	3·5	53·9	3·15
"	H	H	H	Cl	—[3]	Q	218—219	Colourless needles	b	$C_{10}H_7O_2N_2Cl$	54·55	3·4	53·9	3·15
"	H	H	H	Br	—[3]	Q	200—201	Fawn needles	b	$C_{10}H_7O_2N_2Br$	45·3	2·3	44·95	2·6
"	H	CH_3	H	H	44	Q	128—129	Colourless microneedles	b	$C_{11}H_{10}O_2N_2$	65·3	5·0	65·3	5·0
"	H	H	H	CH_3[3]	—	—	116—117	Colourless microneedles	b	$C_{11}H_{10}O_2N_2$	65·25	4·9	65·3	5·0
"	H	CH_3	CH_3	H	55	Q	152—153	Cream microneedles	b	$C_{12}H_{12}O_2N_2$	67·6	6·0	66·65	5·6
"	H	CH_3O	CH_3O	H	32	Q	207—208	Cream microneedles	b	$C_{12}H_{12}O_4N_2$	58·2	5·3	58·1	4·9
"	H	$-[CH_2]_3-$		H	76	Q	115—116	Colourless needles	a	$C_{13}H_{12}O_2N_2$	68·45	5·3	68·4	5·3
"	H	$-[CH_2]_4-$		H	96	Q	135—136	Cream leaflets	b	$C_{14}H_{14}O_2N_2$	69·2	5·85	69·4	5·8
"	H	H	Ac	H[3]	—	—	150—151	Colourless needles	a	$C_{12}H_{10}O_3N_2$	63·0	4·5	62·6	4·35
Ph	H	H	H	H	64	Q	109—110	Colourless needles	a	$C_{15}H_{10}O_2N_2$	71·4	4·1	72·0	4·0
"	NO_2	H	H	H	0	?	175—176	Colourless needles	a	$C_{15}H_9O_4N_3$	61·5	2·7	61·0	3·1
"	H	NO_2	H	H	0	Q	174—175	Buff needles	a	$C_{15}H_9O_4N_3$	61·1	3·15	61·0	3·1
"	H	H	NO_2	H	0	Q	171—172	Pale yellow flakes	d	$C_{15}H_9O_4N_3$	60·8	3·0	61·0	3·1
p-C_6H_4·OMe	H	H	H	H	51	Q	128—129	Pale yellow plates	a	$C_{16}H_{12}O_3N_2$	68·0	4·4	68·6	4·3
2-C_5H_4N	H	H	H	H[3]	—	—	113—114	Pale yellow flakes	b	$C_{14}H_9O_2N_3$	67·0 N, 17·3	4·0	66·9 N, 16·7	3·6

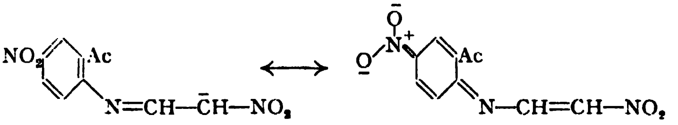
[1] A, dilute NaOH; B, activated alumina; Q, quantitative.
[2] a = Alcohol; *b* = aqueous alcohol; *c* = aqueous acetone; *d* = alcohol–acetone.
[3] See description on p. 403.

detracting from its strength as a pseudo-acid. The importance of the last effect is seen when it is remembered that this mode of cyclisation may involve the anion (VII) of the *aci*-form of (IV). Thus the 5-nitro-group will to a small extent increase the electrophilic nature

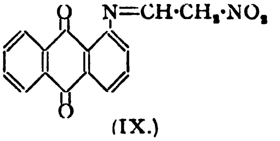


(VII.)

of the carbonyl group, and will greatly strengthen the pseudo-acid by increasing the stability of the anion through resonance (VIII), thus facilitating cyclisation. The 4-nitro-group, whilst having a smaller effect on the strength of the pseudo-acid [cf. the dissociation constants (10^5 K) of benzoic acid (6·27), *p*-nitrobenzoic acid (37·6), and *m*-nitrobenzoic acid (32·1); Watson,



(VIII.)



(IX.)

"Modern Theories of Organic Chemistry," 1941, p. 27], will, on the other hand, exert its main influence by increasing the electrophilic character of the ketone group. In either case, under the faintly alkaline conditions represented by aqueous-acetone solution, cyclisation could be encouraged without serious interference from hydrolysis. With compounds of type (IV), however, electronegative substituents clearly facilitate hydrolysis, so much so that with the *Bz*-nitro-compounds the reaction is so rapid in cold alkali as to forestall cyclisation. In other cases, *e.g.*, that of 2-(*2-nitroethylideneamino*)-*5-methylacetophenone* (IV; R = Me, R_1 = R_3 = H, R_2 = Me), whilst hydrolysis would be slower, the strength of the pseudo-acid will be decreased, as will the electrophilic activity of the ketone group, so that the yield of *3-nitro-4 : 6-dimethylquinoline* actually realised represents only the unpredictable balance of these complicated factors.

Clearly, the most satisfactory type of cyclising agent for use with compounds (IV) would be one which allowed the conversion of the side chain into the ionised *aci*-form, or alternatively was able to cyclise (IV) without ionisation, and in either case did not allow hydroxylic attack at the azomethine linkage. During experiments on the reaction between methazonic acid and *o*-aminoacetophenone it was noticed that quantitative ring-closure of (IV; R = Me, R_1 = R_2 = R_3 = H) to 3-nitrolepidine occurred in aqueous acetone in the presence of activated alumina. This procedure proved applicable, with equal success, in the case of substituted *o*-(2-nitroethylideneamino)acetophenones. Recovery of the substantially pure quinoline derivatives approached the theoretical, even in the cases of (IV; R = Me, R_1 = H, R_2 = H or NO_2, R_3 = NO_2 or H). The only instance among acetophenone derivatives in which a concomitant degree of hydrolysis occurred under this treatment was that of 6-nitro-2-(2-nitroethylideneamino)acetophenone (IV; R = Me, R_1 = NO_2, R_2 = R_3 = H), the yield of *3 : 5-dinitrolepidine* being 75%. This we attribute to steric hindrance between the nitro- and the acetyl group (see below).

The compounds (V), arising from 3-halogeno-2-aminoacetophenones, were also capable of cyclisation to *8-halogeno-3-nitrolepidines* by treatment with alumina. As indicated above, the m. p. of the quinoline corresponded in each case to the second m. p. of the related compound (V).

The ambiguous wording of the original specification (G.P. 335,197) led Hollins ("The Synthesis of Nitrogen Ring Compounds," London, 1924, p. 285) to state that *o*-aminobenzophenone had been utilised in a quinoline synthesis with methazonic acid, but in fact this reaction was not mentioned, and 3-nitro-4-arylquinolines have not been described. Since compounds of the latter type promised to be interesting in several connections, we describe here the reaction of some 2-aminobenzophenones with methazonic acid, reserving for a later paper a description of some reactions of the products obtained.

o-Aminobenzophenone reacted with methazonic acid in acetone–hydrochloric acid to give a high yield of o-(*2-nitroethylideneamino*)*benzophenone*. 2-(*2-Nitroethylideneamino*)-*4′-methoxybenzophenone* was obtained similarly. The nitro-2-aminobenzophenones presented a further interesting parallel to the nitro-2-aminoacetophenones. Thus 3-nitro-2-aminobenzophenone failed to react with methazonic acid, presumably because of hydrogen bonding (VI; R = Ph).

The other isomers provided good yields (Table I) of 4-, 5-, and 6-*nitro*-2-(2-*nitroethylideneamino*)-*benzophenone*, which, as expected, proved to be much less labile than their acetophenone counterparts, surviving crystallisation without becoming cyclised.

(IV; $R = \text{Ph}, R_1 = R_2 = R_3 = \text{H}$) and (IV; $R = p\text{-C}_6\text{H}_4\cdot\text{OMe}, R_1 = R_2 = R_3 = \text{H}$), on dissolution in dilute alkali, were quickly converted into 3-*nitro*-4-*phenyl*- and 3-*nitro*-4-p-*methoxyphenyl-quinoline*, respectively, some hydrolysis also occurring. On the other hand, the nitro-compounds were again completely hydrolysed in these circumstances. Once again, activated alumina proved a valuable cyclisation reagent, and by its aid 4- and 5-nitro-2-(2-nitroethylideneamino)benzophenone, as well as the derivatives of *o*-aminobenzophenone and 2-amino-4′-methoxybenzophenone, were cyclised quantitatively. The poor yield of 3 : 5-*dinitro*-4-*phenylquinoline* arising by alumina cyclisation we again attribute to the steric effect of the nitro-group.

It is interesting that 2-2′-aminobenzoylpyridine reacted with methazonic acid in dilute hydrochloric acid to give 3-*nitro*-4-2′-*pyridylquinoline* directly, presumably because of the increased electrophilic activity of the carbonyl group caused by protonisation of the pyridyl nitrogen atom in acid solution. In contrast 1-aminoanthraquinone provided 1-(2-*nitroethylideneamino*)*anthraquinone* (IX), but no method of cyclising this compound has yet been found; both caustic alkali and alumina effected complete hydrolysis, whilst sodium acetate–acetic anhydride left it unchanged.

Various reactions, absorption spectra, etc., of the products described above will be described in the future, as will be the reaction of methazonic acid with some aniline derivatives.

3-*Iodo*-2-*aminoacetophenone*, used in the present work, was obtained by reducing 3-*iodo*-2-*nitroacetophenone*, prepared by a Sandmeyer reaction on 2-nitro-3-aminoacetophenone. It was characterised by conversion into 8-*iodo*-4-*hydroxycinnoline* on diazotisation.

EXPERIMENTAL.

(M. p.s are uncorrected.)

Materials.—The ketones were obtained by known methods as follows : *o*-Aminoacetophenone, 3-, 4-, 5-, and 6-nitro-2-aminoacetophenone, 5-chloro-, 3-chloro-, and 3-bromo-2-aminoacetophenone (Simpson *et al.*, *J.*, 1945, 646; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405; Schofield and Theobald, *J.*, 1949, 796). 2-Nitro-3-aminoacetophenone (Leonard and Boyd, *loc. cit.*; cf. Schofield and Swain, *J.*, 1949, 1367). 4-Chloro-2-aminoacetophenone (Atkinson and Simpson, *J.*, 1947, 232). 2-Amino-3-methylacetophenone (Simpson, unpublished). 2-Amino-5-methyl-, 2-amino-4 : 5-dimethyl-, 2-amino-4 : 5-*cyclo*penteno-, and 2-amino-4 : 5-*cyclo*hexeno-acetophenone (Schofield, Swain, and Theobald, *J.*, 1949, 2399). 2-Amino-1 : 4-diacetylbenzene (Schofield and Theobald, *ibid.*, p. 2404). 6-Aminoacetoveratrone (Simpson, *J.*, 1946, 94). *o*-Aminobenzophenone (Hewett *et al.*, *J.*, 1948, 292). 2-Amino-4′-methoxybenzophenone (Simpson *et al.*, *loc. cit.*). 2-, 3-, 4-, 5-, and 6-Nitro-2-aminobenzophenone (Schofield and Theobald, unpublished). 2-2′-Aminobenzoylpyridine (Schofield, *J.*, 1949, 2408).

Methazonic acid was prepared as described by Steinkopf (*Ber.*, 1909, **42**, 2031), and the product freed from sodium chloride by extraction with ether.

2-(2-*Nitroethylideneamino*)*aryl Ketones.*—In each case the amino-ketone and methazonic acid were dissolved in water, concentrated hydrochloric acid, and, in some cases, acetone, the solution left overnight, and the product collected and crystallised. The following table, in conjunction with Table I, summarises

Compound.	Wt. of ketone (g.).	Vol. of acetone (c.c.).	Vol. of water (c.c.).	Vol. of conc. HCl (c.c.).	Wt. of crude product (g.).	M. p. of crude product (decomp.).
1	5·0	—	200	15	2·34	109—120°
2	0·2	5	5	1	0·22	180—182
3	2·0	150	25	25	2·17 *	204—206
4	0·5	10	5	5	0·38	207—208
5	1·0	25	25	10	0·9	187—188
6	0·5	10	5	5	0·35	194—196
7	0·2	—	5	1	0·16	188—191
8	0·2	5	5	2	0·14	196—201
9	0·2	—	5	1	0·16	175—180
10	1·0	100	—	20	0·61	216—218
11	1·0	150	5	5	1·09	212—213
12	1·0	20	10	10	1·05	130—133
13	1·0	20	5	10	0·85 *	156—158
14	1·0	30	5	10	0·92	168—170
15	0·5	50	5	5	0·42	175—176
16	1·0	50	50	15	1·04	162—163

* Slight concentration of the solution was effected in isolating the product.

the essential data. Weights of methazonic acid are omitted since in all cases 1 equiv. of this compound, with respect to the amino-ketone, was used. The products are, in general, yellow, highly crystalline substances. Acetone is usually the best solvent for crystallisation, the compounds being but moderately soluble in alcohol, benzene, or chloroform, and almost insoluble in ether or water.

2-(2-*Nitroethylideneamino*)*acetophenone Oximes.*—In these cases the 3-halogeno-2-aminoacetophenones were dissolved in acetone, water, and hydrochloric acid, again with 1 equiv. of methazonic acid, and left for 24 hours. The product (see following table) only separated after dilution with water, or removal of acetone followed by dilution (see Table II).

Compound.	Wt. of ketone (g.).	Vol. of acetone (c.c.).	Vol. of water (c.c.).	Vol. of conc. HCl (c.c.).	Vol. of water added (c.c.).	Wt. of crude product (g.).	M. p. of crude product (decomp.).
17	0·5	10	5	2	20	0·35	171—176°
18	0·2	5	2	1	10	0·10	176—178
19	0·5	5	1	1	10	0·26	138—140

Quinoline Derivatives.—(*a*) The nitroethylideneamino-compounds were stirred with 2N-sodium hydroxide solution, sometimes with gentle warming. In a few cases the substance dissolved, giving a yellow solution which rapidly deposited the quinoline derivative, or more usually deposition began before dissolution was complete. The products were collected and washed with water, whereupon in most cases substantially pure compounds were obtained. For analysis, crystallisation from acetone, aqueous acetone, alcohol, or aqueous alcohol was effected (Table III). Such alkaline treatment of *Bz*-nitro-2-(2-nitroethylideneamino)-compounds led only to recovery of the parent amine. In other cases, partial hydrolysis was indicated by acidification of the reaction liquor, followed by diazotisation and coupling with alkaline β-naphthol. The 3-halogeno-2-(2-nitroethylideneamino)acetophenone oximes dissolved readily in dilute alkali but no precipitate appeared subsequently, and the acidified solution gave no test for a primary amine.

(*b*) An acetone solution of the nitroethylideneamino-compound was treated with 10 parts of activated alumina, and left overnight. Usually the solution lightened in colour during the cyclisation. Filtration from alumina and removal of acetone usually gave the substantially pure product; occasionally slight stickiness was removed by trituration with a little cold ether. In the cases of 6-nitro-2-(2-nitroethylideneamino)acetophenone and the analogous benzophenone, the products, after removal of the acetone, were oily, and the pure quinoline was only isolated with some difficulty, especially in the second case where the parent amine and derived quinoline showed similar solubilities.

3-*Nitro*-7-*acetyl-lepidine.*—A solution of 2-amino-1 : 4-diacetylbenzene (1 g.) and methazonic acid (0·59 g.) in water (50 c.c.) and concentrated hydrochloric acid (10 c.c.) was left for 24 hours, and the precipitate collected, washed, and stirred with dilute alkali. Crude 3-nitro-7-acetyl-lepidine (0·50 g.) separated, and crystallised from alcohol in colourless needles, m. p. 150—151°.

3-*Nitro*-4-2′-*pyridylquinoline.*—A solution of 2-2′-aminobenzoylpyridine (1 g.) and methazonic acid (0·55 g.) in water (10 c.c.) and concentrated hydrochloric acid (5 c.c.) was left overnight, neutralised with sodium acetate, and extracted with chloroform. The dried (Na_2SO_4) extract yielded a sticky solid, crystallising in pale yellow flakes of 3-nitro-4-2′-pyridylquinoline (0·87 g.), m. p. 113—114°.

3-*Nitro*-4 : 8-*dimethylquinoline.*—A solution of 2-amino-3-methylacetophenone (0·1 g.) and methazonic acid (0·07 g.), in acetone (5 c.c.), water (5 c.c.), and concentrated hydrochloric acid (2 c.c.), was left for 24 hours. Removal of the acetone and addition of water precipitated the crude product (0·09 g., m. p. 103—105°), which separated from dilute ethanol in colourless microneedles, m. p. 116—117°.

3-*Iodo*-2-*nitroacetophenone.*—2-Nitro-3-aminoacetophenone (3 g.) in hydrochloric acid (30 c.c. of *ca.* 10N.) was diazotised at 0° with aqueous sodium nitrite (20%). Excess of nitrous acid was destroyed with urea, potassium iodide (3·4 g. in 10 c.c. of water) added, and the product collected after 1 hour. Trituration with a little ether, and crystallisation from benzene–ligroin (b. p. 60—80°), gave the substantially pure product (2·2 g.). 3-*Iodo*-2-*nitroacetophenone* formed buff leaflets, m. p. 97—98° (Found : C, 33·77; H, 2·46. $C_8H_6O_3NI$ requires C, 33·01; H, 2·08%).

3-*Iodo*-2-*aminoacetophenone.*—The above compound (2 g.) in acetic acid (10 c.c.) at 95° was treated with iron powder (1·5 g. added during 1 hour), additions of water (5 × 2 c.c.) being made at 10-minute intervals. After 1 hour more at 95° the mixture, after dilution, yielded to ether the practically pure product (1·51 g.). 3-*Iodo*-2-*aminoacetophenone* formed golden-yellow prisms, m. p. 57—58° (Found : C, 36·41; H, 4·11. C_8H_8ONI requires C, 36·80; H, 3·09%), when crystallised from ether–ligroin (b. p. 40—60°).

8-*Iodo*-4-*hydroxycinnoline.*—The hydrochloride suspension formed from the above amine (0·2 g.) and concentrated hydrochloric acid (5 c.c.) was diazotised at 0° with aqueous sodium nitrite (10%), and the solution left at room temperature for 5 days. The mixture was heated for a short time at 95°, and the precipitate collected (0·04 g.). 8-*Iodo*-4-*hydroxycinnoline* formed pale yellow leaflets, m. p. 261—262° (Found : C, 35·74; H, 1·88. $C_8H_5ON_2I$ requires C, 35·30; H, 1·85%), from ethanol.

Our thanks are due to the Council of University College, Exeter, and to Messrs. Imperial Chemical Industries Ltd. for financial aid, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. S. T.).

WASHINGTON SINGER LABORATORIES,
UNIVERSITY COLLEGE OF THE SOUTH WEST, EXETER.

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NOTES.

The Behaviour of the Copper Electrode in Dilute Copper Sulphate Solutions. By A. A. Mousa.

THE behaviour of the copper electrode in dilute copper sulphate solutions has recently been reported by Tourky and El Wakkad (*J.*, 1948, 749). The potential–activity curves obtained by the authors showed a break which was assumed to signify a pure Cu–Cu$^{\cdot}$ electrode reaction in solutions of cupric-ion activity, $a_{Cu^{\cdot\cdot}}$, lower than $\sim 10^{-4}$. Such an assumption, however, is not justifiable since it would involve a complete breakdown of the equilibrium $Cu^{\cdot\cdot} + Cu \rightleftharpoons 2Cu^{\cdot}$ which should necessarily be maintained whenever metallic copper is in contact with any of its ions in solution. The method to be used to interpret the results and which leads to the above assumption is discussed below, and an explanation for the break observed is put forward.

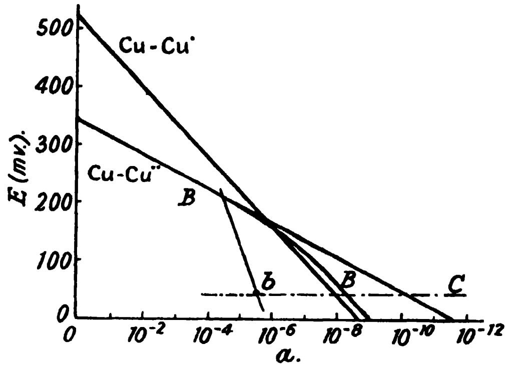
In the first place, the different values assigned to the equilibrium constant K of the reaction $Cu^{\cdot\cdot} + Cu \rightleftharpoons 2Cu^{\cdot}$ were discussed in detail and 10^{-6} was selected as the most suitable value for calculations. Since, however, a true thermodynamic equilibrium should necessarily satisfy the identity of the different potentials Cu–Cu$^{\cdot\cdot}$, Cu–Cu$^{\cdot}$, and Cu$^{\cdot\cdot}$–Cu$^{\cdot}$ in one and the same solution, the use of any particular value for K other than that which is determined by an equation such as

$$E_{0(Cu-Cu^{\cdot\cdot})} + 0{\cdot}030 \log a_{Cu^{\cdot\cdot}} = E_{0(Cu-Cu^{\cdot})} + 0{\cdot}060 \log a_{Cu^{\cdot}}$$

is not permissible and leads to unnecessary complications. With the values chosen for $E_{0(Cu-Cu^{\cdot\cdot})}$ and $E_{0(Cu-Cu^{\cdot})}$, *viz.* 0·3457 and 0·5220 v., respectively, K amounts to $10^{-5{\cdot}877}$. Setting K as 10^{-6} instead of $10^{-5{\cdot}877}$ accounts, although in part only, for the non-identity of the calculated potentials, at least in solutions of high cupric-ion activity where, by subtracting $0{\cdot}5a_{Cu^{\cdot}}$ supposed to be in equilibrium, the original cupric-ion activity remained practically unchanged.

In the second place, the Cu–Cu$^{\cdot\cdot}$ potential in different cupric-ion activities ($a_{Cu^{\cdot\cdot}}$) was calculated as $0{\cdot}5\,(E_{Cu-Cu^{\cdot}} + E_{Cu^{\cdot\cdot}-Cu^{\cdot}})$, a procedure which is valid only if the system is in true thermodynamic equilibrium. That this was not the case with the calculated activities would have readily been revealed if solutions of $a_{Cu^{\cdot\cdot}}$ infinitesimally lower than 10^{-6} had been considered, in which case the Cu$^{\cdot\cdot}$–Cu$^{\cdot}$ potential would have been found to acquire, at a limit, an infinite negative potential.

The reason for such an abnormality, as referred to above, lies undoubtedly in setting $a_{Cu^{\cdot}}(e)$ as equal to $\sqrt{[a_{Cu^{\cdot\cdot}}(o) \times K]}$ instead of $\sqrt{[a_{Cu^{\cdot\cdot}}(e) \times K]}$ where $a_{Cu^{\cdot\cdot}}(o)$ is the original cupric-ion activity, and $a_{Cu^{\cdot\cdot}}(e)$ and $a_{Cu^{\cdot}}(e)$ are respectively the cupric- and cuprous-ion activities at equilibrium. With the equilibrium state represented as such $Cu^{\cdot\cdot} + Cu \rightleftharpoons 2Cu^{\cdot}$, the equation $a_{Cu^{\cdot\cdot}}(o) = a_{Cu^{\cdot\cdot}}(e) + 0{\cdot}5\sqrt{[a_{Cu^{\cdot\cdot}}(e) \times K]}$ should then hold and can be solved for $a_{Cu^{\cdot\cdot}}(e)$ with any known value for $a_{Cu^{\cdot\cdot}}(o)$ as illustrated by the data in the following table.



$a_{Cu^{\cdot\cdot}}(o)$.	$a_{Cu^{\cdot\cdot}}(e)$.	$a_{Cu^{\cdot}}(e)$.	E.	$a_{Cu^{\cdot\cdot}}(o)$.	$a_{Cu^{\cdot\cdot}}(e)$.	$a_{Cu^{\cdot}}(e)$.	E.
$10^{-0{\cdot}9902}$	$10^{-1{\cdot}0000}$	$10^{-3{\cdot}4385}$	+0·3157	$10^{-5{\cdot}8024}$	$10^{-6{\cdot}0000}$	$10^{-5{\cdot}9385}$	0·1657
$10^{-1{\cdot}9975}$	10^{-2}	$10^{-3{\cdot}9385}$	0·2857	$10^{-6{\cdot}5495}$	10^{-7}	$10^{-6{\cdot}4385}$	0·1357
$10^{-2{\cdot}9922}$	10^{-3}	$10^{-4{\cdot}4385}$	0·2557	$10^{-7{\cdot}1700}$	10^{-8}	$10^{-6{\cdot}9385}$	0·1057
$10^{-3{\cdot}9756}$	10^{-4}	$10^{-4{\cdot}9385}$	0·2257	$10^{-7{\cdot}7167}$	10^{-9}	$10^{-7{\cdot}4385}$	0·0757
$10^{-4{\cdot}9273}$	10^{-5}	$10^{-5{\cdot}4384}$	0·1957	$10^{-8{\cdot}7368}$	10^{-10}	$10^{-7{\cdot}9385}$	0·0457

N.B.—In obtaining these results the equation was solved by fixing values for $a_{Cu^{\cdot\cdot}}(e)$; the corresponding values for $a_{Cu^{\cdot\cdot}}(o)$ were then calculated. K was set as $10^{-5{\cdot}877}$.

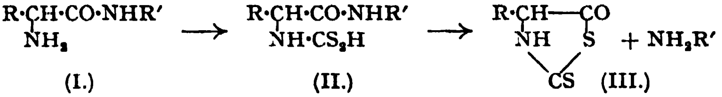
The above derived activities stand, no doubt, for true thermodynamic equilibria through which the identity of the different potentials is satisfied. Hence, the copper electrode potential, E (column 4), can be readily deduced from any of the following equations:

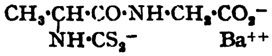
$$\begin{aligned} E &= E_{0(Cu-Cu^{\cdot\cdot})} + 0{\cdot}030 \log a_{Cu^{\cdot\cdot}}(e) \\ &= E_{0(Cu-Cu^{\cdot})} + 0{\cdot}060 \log a_{Cu^{\cdot}}(e) \\ \text{or } &= E_{0(Cu^{\cdot\cdot}-Cu^{\cdot})} + 0{\cdot}060 \log a_{Cu^{\cdot\cdot}}(e)/a_{Cu^{\cdot}}(e) \end{aligned}$$

Now, by plotting E against $a_{Cu^{\cdot\cdot}}(o)$ the theoretical curve B–B, shown in the figure, is obtained, manifesting a break which possesses its own slope and does not coincide with that for the pure Cu–Cu$^{\cdot}$ system. It should be emphasised, however, that the trend of the curve depends in the first place on the non-appearance of a solid phase that would participate in an ion-determining system, which is hardly the case with aqueous solutions. According to Tourky and El Wakkad's findings (*J.*, 1948, 740), the precipitation pH value of CuOH at a protected copper surface is $\sim$6·8, a value which necessarily approximates to that of the most dilute solution used ($a_{Cu^{\cdot\cdot}} \sim 10^{-5{\cdot}5}$). As denoted by the theoretical curve B–B, the $a_{Cu^{\cdot}}(e)$ at this dilution is $\sim 10^{-5{\cdot}8}$. The product $a_{Cu^{\cdot}} \times a_{OH'}$ thus exceeds the solubility product S of CuOH which will then be precipitated with consequent lowering of $a_{Cu^{\cdot}}$ to $S/a_{OH'}$ or $\sim 10^{-8}$ (with 10^{-15} as the most probable value for S). The cuprous-ion activity is thus fixed through the separation of CuOH and will be kept at the above value as long as the pH remains constant. Any excess of cupric ion over that necessary to maintain the equilibrium state (horizontal line *C*) will be reduced at the metal surface to cuprous, a process which will lead only to the further development of the solid phase separated. The potential, on the E–$a_{\mathrm{Cu}''}(o)$ plot, will then be denoted by the point *b*. The trend of the break manifested thereby is not at all comparable with that for the pure Cu–Cu' system; hence its extrapolation to meet the potential axis is insignificant. The author is pleased to know that Prof. Tourky agrees to the above amendment which explains adequately the conclusions in the original paper.—FACULTY OF SCIENCE, FOUAD I UNIVERSITY, ABBASSIA, CAIRO, EGYPT. [*Received, June 16th*, 1949.]

The Removal of Terminal Groups from Peptides. By A. L. LEVY.

COOK, HEILBRON, AND LEVY (*J.*, 1948, 201) described the first example of an unusual reaction of α-amino-amides, namely the cyclisation of *N*-dithiocarboxyglycine amide (II; R = R' = H) with cold mineral acid to give 2-thiothiazolid-5-one (III; R = H) in high yield, with resulting fission of the peptide linkage. An analogous series of transformations has since been carried out with the amides of DL-phenylalanine and DL-phenylglycine (Billimoria and Cook, *J.*, 1949, 2323), DL-alanine (Cook and Levy, in the press), and L-tyrosine, L-leucine, DL-methionine, DL-norleucine, L-glutamine, DL-α-amino*iso*butyric acid and DL-aminomalonic acid (Davis and Levy, to be published). A particularly interesting example of this reaction arises when NH_2R' represents an amino-acid or peptide, in which case it should provide a method for the removal, and identification, of the terminal group in the peptide or polypeptide (I). This possibility has now been realised in the following four examples.


(I.) (II.) (III.)


$\underset{\displaystyle NH\cdot CS_2^-}{CH_3\cdot CH}\cdot CO\cdot NH\cdot CH_2\cdot CO_2^- \quad Ba^{++}$

(IV.)

DL-Alanylglycine in 2 equivalents of 0·34N-barium hydroxide was shaken with carbon disulphide for 19 hours at room temperature, whereafter evaporation afforded the colourless *barium* salt (IV). This was acidified with N-hydrochloric acid to pH 3—4 to give 2-thio-4-methylthiazolid-5-one (III; R = Me) in 75% yield. Similarly, when DL-alanylglycylglycine was shaken with carbon disulphide and 0·34N-barium hydroxide, acidification of the resulting solution gave (III; R = Me). Glycylglycine was condensed with carbon disulphide as in the two previous examples, whereafter acidification precipitated 2-thio-5-thiazolidone (III; R = H) in 51% yield. DL-Phenylalanylglycine in 2 equivalents of N-potassium hydroxide was combined with carbon disulphide at room temperature, whereafter addition of hydrochloric acid caused the separation of 2-thio-4-benzylthiazolid-5-one (III; R = CH_2Ph).

Finally, it is interesting to note that Léonis (*Compt. rend. Lab. Carlsberg, Sér. Chim.*, 1948, **26**, 315) has utilised the reaction of amino-acids and peptides with carbon disulphide in a quantitative manner to determine the number, and to a limited extent the type, of terminal amino-groups present. In combination with the above results, this should provide a useful method for elucidating the amino-acid sequence in peptides, and this possibility is being investigated.

A preliminary account of another method for the determination of amino-acid sequences, which involves removal of the terminal residue under anhydrous acid conditions as a 3-phenyl-2-thiohydantoin, has been described by Edman (1st. International Congress of Biochemistry, Cambridge, 1949; *Arch. Biochem.*, 1949, **22**, 573).

Experimental.—DL-Alanylglycine (Cook and Levy, in the press) (0·584 g.) in 0·339N-barium hydroxide (23·6 c.c., 2 equivs.) was shaken with carbon disulphide (1 c.c.) for 19 hours in a nitrogen atmosphere, and the resulting orange solution (pH 9) decolorised with a stream of carbon dioxide, which also removed a little free barium hydroxide as barium carbonate. Evaporation in a vacuum yielded *barium* (N-*dithiocarboxyalanyl*)*glycine* (IV), which recrystallised from aqueous ethanol as a colourless, microcrystalline powder, m. p. above 280°, and was dried at 100°/0·1 mm. (Found: C, 19·4; H, 3·7; N, 7·6. $C_6H_8O_3N_2S_2Ba$ requires C, 20·1; H, 2·2; N, 7·8%). The barium salt (1·45 g.) in water (8 c.c.) was acidified with N-hydrochloric acid (8 c.c.) (pH then 3), whereupon 2-thio-4-methylthiazolid-5-one (III; R = Me) crystallised in needles, m. p. 125—126° (0·45 g., 75%). When acidification was effected with acetic acid, (III; R = Me) separated more slowly, and in poorer yield.

DL-Alanylglycylglycine (Fischer, *Ber.*, 1903, **36**, 2982) (0·61 g.) in 0·339N-barium hydroxide (18 c.c., 2 equivs.) was shaken with carbon disulphide (1 c.c.) for 18 hours in a nitrogen atmosphere, and the yellow-orange solution acidified with 2N-hydrochloric acid (3·2 c.c.). Extraction with ethyl acetate, after drying and evaporation, yielded 2-thio-4-methylthiazolid-5-one, m. p. 122—125°.

Glycylglycine (Freudenberg, *Ber.*, 1932, **65**, 1191) (0·66 g.) in 0·339N-barium hydroxide (29·5 c.c., 2 equivs.) was shaken with carbon disulphide (1 c.c.) for 22 hours at room temperature, under nitrogen. The solution went through a maximum orange colour and then became yellower, and a little hydrogen sulphide was produced. A portion (10·5 c.c.) was acidified with concentrated hydrochloric acid (2·5 c.c.), whereupon 2-thiothiazolid-5-one (III; R = H) separated slowly; the solution and crystals were extracted with ethyl acetate to secure the full yield (0·12 g., 51%). The remainder of the dithiocarbamate solution (pH 8) was saturated with carbon dioxide (pH then 6·5), and evaporated to dryness in a vacuum to give yellow barium (*N*-dithiocarboxyglycyl)glycine, which could be precipitated cleanly from aqueous ethanol. It exhibited a bright red fluorescence in ultra-violet light.

DL-Phenylalanylglycine was conveniently synthesised by the procedure of Wessely and Sigmund (*Z. physiol. Chem.*, 1926, **157**, 91) from DL-anhydro-*N*-carboxyphenylalanine and glycine, the former reagent being prepared by an improved method (Levy, *Nature*, in the press). Thus, DL-phenylalanine (4 g.) was suspended in a solution (40% w/w) of carbonyl chloride in toluene (150 c.c.) and gently heated until refluxing. After boiling for a further 4 hours, the clear solution was cooled to 0°, and DL-anhydro-*N*-carboxyphenylalanine (2·7 g.), m. p. 125°, collected. A further 0·5 g. (total yield, 69%), m. p. 124°, was obtained by concentration of the filtrate. In another preparation, phenylalanine (1·0 g.) was heated under reflux with carbonyl chloride in toluene (10% w/w; 25 c.c.) for 1·25 hours, whereafter the carboxy-anhydride (0·75 g.) crystallised, on cooling, in large blades, m. p. 128—129° to a clear liquid which evolved carbon dioxide vigorously at ~155°. A further 0·06 g. (total yield, 70%), m. p. 127—128°, was obtained from the filtrate.

The peptide (0·3 g.) in 1·1N-potassium hydroxide (2·7 c.c., 2·2 equivs.) was shaken with carbon disulphide (0·5 c.c.) for 3 hours in nitrogen, and the resulting solution extracted with ether, cooled to 0°, and acidified with concentrated hydrochloric acid (10 drops). 2-Thio-4-benzylthiazolid-5-one separated as a gum which slowly solidified, and recrystallised from ethanol in needles, m. p. 159°.

The author is grateful to Sir Ian Heilbron, D.S.O., F.R.S., and Dr. A. H. Cook for their helpful interest in this work, and to the Department of Scientific and Industrial Research for a Senior Research Award.—Imperial College of Science and Technology, S. Kensington, London, S.W.7. [*Received, August 24th*, 1949.]

The Action of Copper on Some Aryldiazonium Sulphates, and the Isolation of Copper Salts.

By Herbert H. Hodgson and John Habeshaw.

In view of the recent paper by Cowdrey and Davies (*J.*, 1949, S 48) in which the formation of copper complexes in the Sandmeyer reaction has been reported, some work done by us on a modified Gattermann reaction during 1935—1937 is of interest. It was found that, when copper reacted with aryldiazonium sulphates, deamination occurred to an extent which varied according to the amine employed, and also that the amount of phenol (or naphthol) which could be directly isolated by steam-distillation was generally less than expected. The steam-distillation residues contained copper compounds which were sparingly soluble in boiling water and were decomposed by alkali to give the phenol or naphthol. It would appear, therefore, that the low yield of phenol or naphthol could be accounted for in part by these copper salts. The salts are usually white, or yellow in the case of the nitro-compounds, do not melt but sinter and decompose when heated, and are attacked slowly by cold mineral acids, which become green, while the solid discolours and in some cases becomes black. Unfortunately, only analyses for the copper content of these materials are available but, as can be seen from the table, these correspond to the structure Ar·O·Cu. These and other reaction products are recorded in the table below.

Experimental.—Preparation of the reduced copper. A solution of crystallised copper sulphate (50 g.) in hot water (500 c.c.) was stirred with zinc dust (15 g.), added gradually, and the precipitated copper filtered off and washed.

General reaction procedure. A solution of the amine (5 g.) in sulphuric acid (25 c.c.; *d* 1·84) and water (150 c.c.) was diazotised below 5° with the calculated amount of sodium nitrite in water, the excess of nitrous acid removed by urea, and the mixture treated gradually at room temperature with the copper paste (rather than *vice versa*) to avoid the copper surface becoming coated with reaction products; the mixture was kept overnight, and then steam-distilled to remove the deaminated product (phenol or naphthol) and any volatile diaryl such as diphenyl. The steam-distillate was made alkaline and extracted with ether to remove all but the phenols, and then acidified cold with sulphuric acid and again extracted with ether to remove the latter. The steam-distillation residue was repeatedly extracted with hot water and the extracts were filtered hot; on cooling there separated, after several hours, white or yellow copper compounds of the respective phenol or naphthol. The final residue was extracted with hot aqueous sodium hydroxide to decompose any remaining copper compounds, washed with water, dried, and boiled with benzene to remove non-volatile diaryls and azo-compounds. In the cases of the nitro-naphthylamines, the products listed as (1) in the table are those obtained by the addition of copper to the solutions obtained after their diazotisation by the glacial acetic–nitrosylsulphuric acid procedure (Hodgson and Walker, *J.*, 1933, 1620), whereas the products listed as (2) are those obtained after dilution of the acid mixture with ice (100 g.).

Reaction Products (in g.) from Individual Amines (5 *g.*).

(The amounts are the mean of three experiments.)

Diazonium sulphate.	Deaminated product.	Azo-compound.	Free phenol or naphthol.	Total diaryl or dinaphthyl.	Copper compound.		
					Yield.	Cu, %.	Cu, calc. %.
Benzene	—	0·2	0·5	0·3	None	—	—
o-Chlorobenzene	0·25	1·2	0·1	—	0·25	32·6	33·0
,,	0·6	2·0	0·2	—	0·25	32·8	33·0
o-Nitrobenzene	0·2	—	0·5	2·5	0·25	32·3	31·3
,,	0·4	—	0·6	2·0	0·3	32·7	31·3
,,	0·3	—	0·6	2·5	0·3	32·5	31·3
p-Toluene	0·65	0·48	0·8	—	None	—	—
Naphthalene-1	0·1	—	0·4	—	None	—	—
Naphthalene-2	0·2	—	2·1	—	None	—	—
4-Chloronaphthalene-1	—	2·4	0·5	—	0·5	26·0	26·2
1-Chloronaphthalene-2	—	2·0	0·4	—	0·4	25·8	26·2
2-Nitronaphthalene-1	0·7 (1) 0·25 (2)	1·0 (1)	0·5	1·3 (2)	0·8	25·8	25·1
4-Nitronaphthalene-1	0·4 (1) 0·15 (2)	1·5 (1)	0·2	2·0 (2)	0·3	26·0	25·1
1-Nitronaphthalene-2	0·5 (1) 0·15 (2)	1·5 (1)	0·2	1·3 (2)	0·3	25·9	25·1

In each case, the copper compound was ignited with nitric acid and the copper weighed as oxide after ignition.

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division for gifts of chemicals.—
TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, September 22nd*, 1949.]

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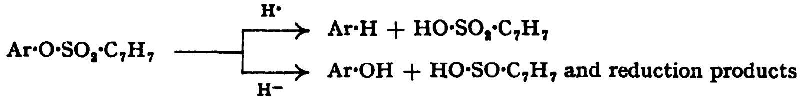
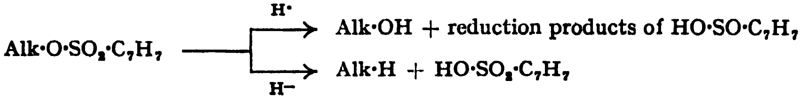
*The Reduction of Toluene-*p*-sulphonic Esters.* By G. W. KENNER and M. A. MURRAY.

THE reduction of toluene-*p*-sulphonic esters has recently been studied by Schmid and Karrer (*Helv. Chim. Acta*, 1949, **32**, 1371) using lithium aluminium hydride and by ourselves (*J.*, 1949, S 178) using Raney nickel and hydrogen; the results of these two investigations form an interesting contrast. Whereas the customary hydrogenation converts the aryl toluenesulphonates into aromatic hydrocarbons, and the alkyl esters into alcohols, lithium aluminium hydride, in general, yields phenols and de-oxygenated aliphatic compounds respectively. As we remarked in our paper, this latter mode of fission is in line with the well-known heterolytic decompositions of toluene-*p*-sulphonic esters by nucleophilic reagents, and Schmid and Karrer (*loc. cit.*) have also drawn attention to the analogy between the reactions of lithium aluminium hydride and those of the Grignard reagents. It is therefore suggested that these reductions may be represented as follows, lithium aluminium hydride being regarded as a source of potential hydride ions :



$$Ar{\cdot}O{\cdot}SO_2{\cdot}C_7H_7 \begin{cases} \xrightarrow{H^{\cdot}} Ar{\cdot}H + HO{\cdot}SO_2{\cdot}C_7H_7 \\ \xrightarrow[H^{-}]{} Ar{\cdot}OH + HO{\cdot}SO{\cdot}C_7H_7 \text{ and reduction products} \end{cases}$$



$$Alk{\cdot}O{\cdot}SO_2{\cdot}C_7H_7 \begin{cases} \xrightarrow{H^{\cdot}} Alk{\cdot}OH + \text{reduction products of } HO{\cdot}SO{\cdot}C_7H_7 \\ \xrightarrow[H^{-}]{} Alk{\cdot}H + HO{\cdot}SO_2{\cdot}C_7H_7 \end{cases}$$

The already publicised reactions of lithium aluminium hydride, for example with carbonyl groups (see, *inter alia*, Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197, 2548) and epoxides (see, *inter alia*, Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1885), as well as the characteristic inertness of unpolarised double bonds to this reagent are in accord with this interpretation. Further, at the suggestion of Professor V. Prelog, one of us allowed lithium aluminium hydride to react with strychnine methosulphate and found the major product to be strychnidine. That is, the amide linkage had been reduced and the methyl group, which is more susceptible to S_N2 reactions than the higher alkyl groups (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 607), had been displaced :

$$\gtrdot N^{+} - CH_3 \xrightarrow{H^{-}} \gtrdot N + CH_4$$

The exceptional cases of 3-toluene-*p*-sulphonyl 1 : 2-5 : 6-di*iso*propylidene glucose and 1-toluene-*p*-sulphonyl 2 : 3-4 : 5-di*iso*propylidene fructose (Schmid and Karrer, *loc. cit.*) may well be examples of steric hindrance in such reactions.

Strychnidine.—Strychnine methosulphate (Clemo, Perkin, and Robinson, *J.*, 1927, 1589) (4·60 g.) was added during 15 minutes to lithium aluminium hydride (1·14 g.) in tetrahydrofuran (25 c.c.) with cooling. The mixture was shaken for ½ hour without cooling and then heated to boiling during 1½ hours before being poured into ice-water (70 c.c.). Chloroform (50 c.c.) was then added, the solid filtered off, and the filtrate extracted with chloroform after being made alkaline with ammonia. The solid was stirred with 3 portions of chloroform, and the combined extracts of the aqueous and the solid phase were dried and evaporated. Recrystallisation of the resulting solid (2 g.) from ethoxyethanol yielded strychnidine, m. p. 258° (in vac.; corr.) (undepressed by an authentic specimen), $[\alpha]_D^{19}$ $-63° \pm 3°$ (*c*, 1·5 in chloroform) (Found, in material sublimed at 150°/0·01 mm. : C, 78·5; H, 7·45. Calc. for $C_{21}H_{24}O_2N_2$: C, 78·7; H, 7·55%). UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE, and ROYAL HOLLOWAY COLLEGE, UNIVERSITY OF LONDON. [*Received, October 14th*, 1949].

The Preparation of 2-Ethoxyethyl Chloride and Bromide. By D. E. AMES and R. E. BOWMAN.

IN connection with another investigation we wished to prepare certain 2-alkoxyalkyl halides. There are many examples in the literature of such preparations, differing, however, very considerably with respect to the yields obtained. Bennett and his co-workers (*J.*, 1925, **127**, 1279; 1927, 270, 472), L. I. Smith *et al.* (*J. Org. Chem.*, 1939, **4**, 334), and Hurd and Fowler (*J. Amer. Chem. Soc.*, 1939, **61**, 249) used the appropriate thionyl halide in the presence of a base (Darzens, *Compt. rend.*, 1911, **152**, 1314). Use of phosphorus tribromide has been described by Palomaa and Kenetti (*Ber.*, 1931, **64B**, 797), Harrison and Diehl (*Org. Synth.*, **23**, 32), Chalmers (*Canadian J. Res.*, 1932, **7**, 464), and Hurd and Fowler (*loc. cit.*) for the same purpose.

We employed the readily available 2-ethoxyethanol as model substance using Darzens's method with thionyl chloride and bromide under conditions described by Gerrard (*J.*, 1939, 100), and thereby obtained excellent, reproducible yields. Furthermore, we have confirmed the finding that the use of more than one molecular proportion of base reduces the yield although excess of thionyl halide is not deleterious.

The following method gave the best results: a mixture of the dry, purified base (1 mol.) and 2-ethoxyethanol (1 mol.) was cooled to −20° and the appropriate thionyl halide (1·1 mols.) added with stirring at such a rate that the temperature did not rise above 0°. The reaction mixture was then allowed to warm to room temperature and thereafter heated at 100° (bath) for 2 hours. When cold, it was treated with dilute hydrochloric acid, and the product isolated with ether. The ethereal extracts were washed with dilute sodium hydroxide solution and dried (Na_2SO_4), and the solvent was removed by careful distillation through a Vigreux column. The product was then obtained by distillation of the residue. In this manner 2-ethoxyethyl chloride was obtained (yields in parentheses) by use of dimethylaniline (61%), pyridine (80%), or quinoline (84%). The bromide was obtained in 70% yield with pyridine as base.

With dimethylaniline as base, an increase in the proportion of thionyl chloride (3 mols.) was without significant effect on the yield of product. Excess of base, *viz.*, 2-ethoxyethanol (1 mol.), dimethylaniline (2 mols.), and thionyl chloride (3 mols.), under the same conditions reduced the yield of chloride to 40%.

We are indebted to the Medical Research Council for a grant which has enabled one of us (D. E. A.) to take part in this work.—BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, October 21st,* 1949.]

Diterpenes. Part II. The Optical Rotation of Hosking's Kaurene. By LINDSAY H. BRIGGS and W. I. TAYLOR.

HOSKING (*Rec. Trav. chim.*, 1928, **47**, 578; 1930, **49**, 1036) described a diterpene, kaurene, m. p. 57—58°, from the essential oil of *Agathis australis* (" kauri "), and its hydrochloride, m. p. 110—111°, from which the hydrocarbon was regenerated by the action of alcoholic potassium hydroxide. It has been shown in Part I (*J.*, 1948, 1888) that the diterpene occurring in the oil has a lower m. p. (50°) and that it is isomerised to *iso*kaurene, m. p. 64°, on treatment of its hydrochloride with alkali. Both kaurene and *iso*kaurene form the same hydrochloride and dihydro-derivative, typical of compounds whose isomerism is caused by the change of the double bond from an exocyclic to an endocyclic position. The m. p.s of Hosking's products are intermediate between those of kaurene and *iso*kaurene and it would appear that in both cases he was dealing with an impure form of *iso*kaurene.

A larger discrepancy occurs, however, in the optical rotation of Hosking's and our product. Although Hosking's liquid diterpene fraction from which the kaurene was isolated was optically active, all the rotations observed on solid products derived therefrom had zero values. On the other hand, all our products had definite lævorotations (*loc. cit.*). With the number of asymmetric centres present in any tetracyclic structure possible for kaurene on an isoprene plan (possibly five) it is difficult to see how racemisation of all centres had occurred in Hosking's manipulation.

Through the courtesy of Professor L. Ruzicka, to whom we express our thanks, we have been able to re-examine an original sample of dihydrokaurene obtained by Hosking. No sample of kaurene remained but the dihydro-derivative on crystallisation from acetic acid had m. p. and mixed m. p. 86°, with $[\alpha]^{21}_{D}$ $-32° \pm 2°$ (*c*, 2·0 in chloroform) in agreement with that recorded by Briggs and Cawley in Part I (*loc. cit.*), *viz.*, $[\alpha]^{20}_{D}$ $-35{\cdot}7°$ (*c*, 0·33 in chloroform), from which we conclude that the original kaurene was active also.

No adequate explanation can be advanced to explain these contrasting results.

One of us (W. I. T.) is indebted for a National Research Scholarship of New Zealand.—AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND; and EIDG. TECHNISCHEN HOCHSCHULE, ZÜRICH. [*Received, November 14th,* 1949.]

Dimorphism in Acenaphthene-3-aldehyde. By JOHN H. GORVIN.

THE aldehyde prepared from acenaphthene by the Gattermann synthesis was reported by Hinkel, Ayling, and Beynon (*J.*, 1936, 344) to melt at 87°; subsequently Fieser and Jones (*J. Amer. Chem. Soc.*, 1942, **64**, 1666) obtained by the *N*-methylformanilide—phosphorus oxychloride procedure a substance, m. p. 107·4—108°. Each of these products gave evidence of being acenaphthene-3-aldehyde.

In the present investigation no difficulty was encountered in the preparation of acenaphthene-3-aldehyde, m. p. 107—107·5° (corr.), by either method. It was therefore of interest to examine the product obtained by the earlier workers, and I am very grateful to Dr. L. E. Hinkel and Mr. E. E. Ayling, of University College, Swansea, for making available a specimen of their original crude aldehyde. The principal contaminant of this material proved to be a very small amount of tar which was difficult to remove completely by crystallisation from light petroleum (b. p. 60—80°); the crystals obtained had m. p. 87°. When however the warm petroleum solution was filtered through activated alumina held in a sintered-glass Büchner funnel the clear filtrate deposited crystals, m. p. 107—107·5°, of authentic acenaphthene-3-aldehyde. A similar product was obtained on hydrolysis of the anil, m. p. 97°, prepared by the Swansea workers (*loc. cit.*) from their aldehyde, m. p. 87°.

In preparations of the aldehyde carried out in these Laboratories the light-petroleum mother-liquor on one occasion deposited crystals, m. p. 85°, showing no melting-point depression on being mixed with the material of Hinkel, Ayling, and Beynon (*loc. cit.*). This substance similarly crystallised as the high-m. p. form after filtration of its light-petroleum solution through alumina.

As the amount of tarry material present in the crude aldehyde was quite inadequate to account for a melting-point lowering of 20° it was concluded that the impurity had stabilised a polymorphic modification of the aldehyde and had inhibited the change to the stable, high-m. p. form which would be expected to occur on fusion or long storage. Confirmation of this was obtained by undisturbed cooling of pure molten acenaphthene-3-aldehyde; often the melt crystallised rapidly to give the high m. p. form but sometimes it could be successfully supercooled with eventual solidification to a crystalline mass, m. p. *ca.* 89°, fusion of which was usually followed by crystallisation of the melt in the form, m. p. 107—107·5°.

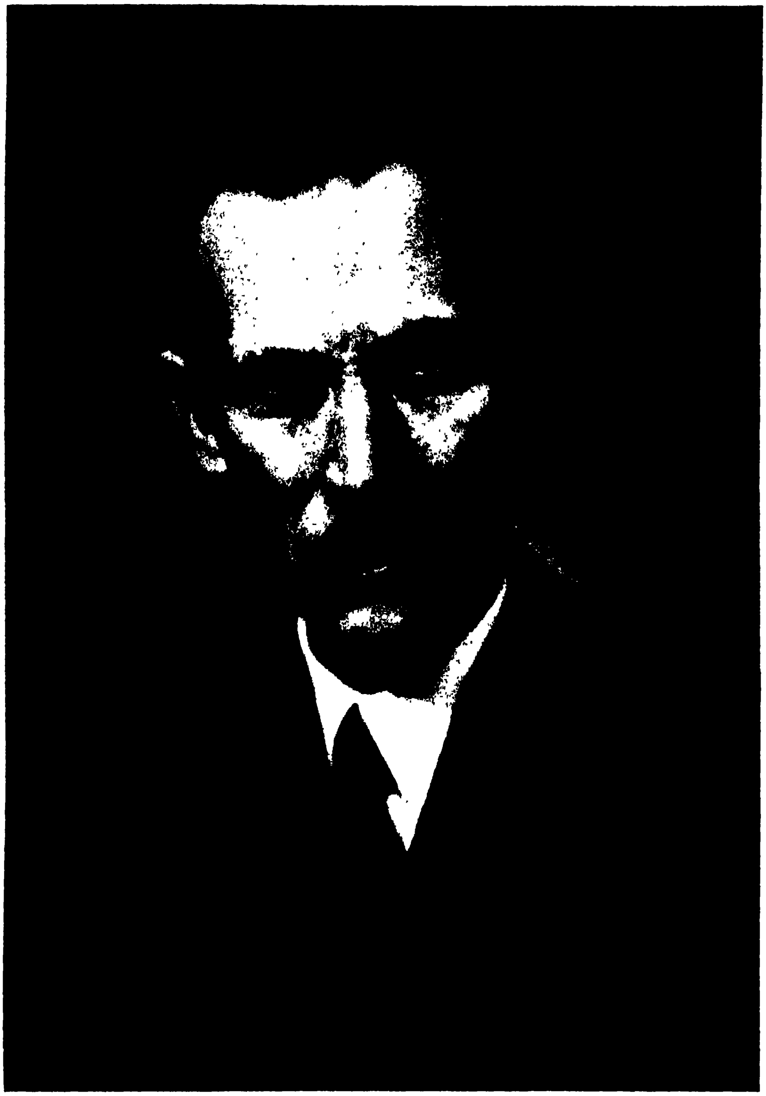
The ease of conversion of the metastable into the stable form of the pure aldehyde is in striking contrast to the persistence of the low-melting form in its contaminated state. A rather similar case has previously been noted (Gorvin, *J.*, 1945, 734) in ethyl 3-sulphanilamidobenzoate; the form, m. p. 105°, recorded by an earlier group of workers persisted until the compound was carefully purified, whereupon conversion into a stable form, m. p. 153°, occurred immediately on fusion at the lower temperature. These examples of metastable states stabilised by impurities emphasise the importance of removal of all traces of contaminating tarry material from organic substances before recording physical constants; the increasing availability of activated adsorbents has in many cases greatly simplified this procedure.—WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, N.W.1. [*Received, November* 18*th*, 1949.].

Synthetic Ribonucleoside-2′ Phosphates: a Correction. By D. M. BROWN, L. J. HAYNES, and A. R. TODD.

IN a recent paper Michelson and Todd (*J.*, 1949, 2476) described the synthesis of a number of mononucleotides derived from the natural ribonucleosides, adenosine, guanosine, cytidine, and uridine. In the course of this work the benzylidene derivatives of adenosine and guanosine were phosphorylated and the protecting groups subsequently removed, yielding products which were assumed to be adenosine-2′ phosphate and guanosine-2′ phosphate. This assumption appeared to be warranted on the evidence that (i) the condensation product of guanosine with benzaldehyde was shown by Bredereck and Berger (*Ber.*, 1940, **73**, 1124) and by Gulland and Overend (*J.*, 1948, 1380) to be 3′ : 5′-benzylidene guanosine, and (ii) the behaviour of the products on acid hydrolysis was analogous to that of the substances described in the literature as uridine-2′ phosphate (Gulland and Smith, *J.*, 1947, 338) and cytidine-2′ phosphate (Gulland and Smith, *J.*, 1948, 1527), the two latter compounds having been prepared in strictly analogous fashion from benzylidene uridine and benzylidene cytidine.

Further investigation has shown, however, that the product we described as adenosine-2′ phosphate is in fact essentially adenosine-5′ phosphate; the latter compound can be isolated in high yield from the amorphous nucleotide described by Michelson and Todd (*loc. cit.*) and has been identified by periodate titration (absorption of 1 mole of oxidant/mole) and by comparison of chemical and physical properties including *X*-ray diffraction photographs. In the same way it has been found that the alleged cytidine-2′ phosphate of Gulland and Smith (*loc. cit.*), as prepared by us, is in fact cytidine-5′ phosphate. From the method of preparation and particularly from consideration of their acid hydrolysis curves, there can be little doubt but that the products described as uridine-2′ phosphate (Gulland and Smith, *loc. cit.*) and guanosine-2′ phosphate (Michelson and Todd, *loc. cit.*) also consist essentially of the corresponding 5′-phosphates.

The origin of 5′-phosphorylated nucleosides in these synthetic experiments is not yet clear but their production would seem to indicate either that a facile and unsuspected migration of acyl groups occurs at some intermediate stage or that the experimental evidence for the 3′ : 5′-structure of the benzylidene nucleosides (Gulland and Overend, *loc. cit.*) is not valid. If the former explanation should prove correct, the finding might well be of significance in the interpretation of nucleic acid structure based on hydrolytic studies. The whole question is at present being investigated in this laboratory, together with the problem of the synthesis of the true nucleoside-2′ phosphates and our results will be communicated in detail later. It seems, however, desirable at this stage to draw attention to the fact that the synthetic nucleotides described in the literature as nucleoside-2′ phosphates do not have the structure assigned to them, the more so as the recent findings of Carter and Cohn (*Fed. Proc.*, 1949, **8**, 190) have aroused interest in nucleoside-2′ phosphates as possible hydrolysis products of yeast ribonucleic acid.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December* 5*th*, 1949.]



J. N. Brönsted

[*To face p.* 400.

The Brönsted Memorial Lecture.

Delivered before the Chemical Society in London on February 3rd, 1949.

By R. P. Bell, M.A., F.R.S.

It is a difficult task to commemorate and appraise a great man like Brönsted, especially for one thirty years his junior in age, and so much his junior in science. This difficulty is increased by a difference in nationality, and I feel therefore that I ought to begin by acknowledging my debt to the many friends in Denmark who have helped me in the preparation of this lecture. I must mention especially Mrs. Brönsted, who has provided me with much material, especially about Brönsted's early life, and Professor Christiansen, who has made available to me the manuscript of his own memorial lecture to Brönsted. What I have to say owes a very great deal to their willing co-operation.

I shall begin by giving an outline of Brönsted's life and career, followed by some account of his scientific work, and finally I shall try to give a general picture of him as a scientist and as a man.

Johannes Nicolaus Brönsted was born on February 22nd, 1879, in Varde, a small town in West Jutland. His father was a civil engineer employed by " Hedeselskabet," a corporation founded to reclaim moorland by draining, irrigation, and planting. His mother died shortly after his birth, but his father remarried shortly afterwards, and the family moved to a farm in the heart of Jutland, where the young Brönsted and his elder sister spent most of their childhood. This period laid the foundation for the love of country things and country people which played such a great part in his later life. When he was twelve years old his family moved to Aarhus, the second largest city in Denmark, but still an essentially rural environment. He went to school there and seems to have been an apt pupil, particularly in mathematics. There was, of course, no school instruction in chemistry at that time, but Brönsted's interest in the subject was a very early one, his first source of information being an agricultural dictionary which he found in the attic. He did primitive experiments at home in the usual fashion, and the spirit lamp and balance which he used are still in existence.

His father died, in 1893, leaving the family in straitened circumstances. Several friends of the family felt that the young Brönsted ought to begin to earn his living, but his mother recognised his promise and was determined to give him and his sister a good education even if it meant considerable sacrifices. The family moved to Copenhagen, and Brönsted attended the Metropolitan School there, where he found not only a high educational standard, but also a remarkably stimulating set of school-fellows. Of the twenty boys in his class, two became bishops, two distinguished physicians, and five professors. One of the latter was Niels Bjerrum, his closest friend for many years, and his chief rival in making Danish physical chemistry world-famous. Brönsted matriculated in 1897, and went to study at the Polytechnic Institute in Copenhagen, where he met Charlotte Louise Warberg, whom he married in 1903. His studies seem to have sat lightly on his shoulders, and he found plenty of leisure to cultivate other interests such as philosophy, art, poetry, and music. It was at first intended that he should become an engineer like his father, but after taking his first degree in that subject in 1899 he changed over to pure science, and took his " Magister " degree in chemistry in 1902. At that date this degree was something of a rarity, especially in chemistry, and Brönsted's friends used " Magister " as a nickname for many years afterwards.

There was no academic position immediately available, and Brönsted worked for a short time in an electro-technical concern. However, he soon returned to the University Chemical Laboratory, and was made an assistant there in 1905. He worked there on his affinity measurements, and in May 1908 presented the third paper in this series (on mixtures of sulphuric acid and water) for his doctorate degree. In the same year a new chair of chemistry was instituted in Copenhagen which combined the duties of teaching physical chemistry to the University students, and inorganic chemistry to students at the Polytechnic Institute. The two competitors for this chair were Brönsted and Niels Bjerrum, who had been Brönsted's class-mate at school, and had taken his doctorate degree in the same year. It must have been a very difficult decision for the judges to make, but their choice finally fell on Brönsted, who was appointed at the early age of 29. The news reached the Brönsted family in a dramatic way: one day just before Christmas a goods train stopped at the bottom of their garden in the country, and a railway official descended bearing a telegram of congratulation from Bjerrum.

This appointment fixed the whole of Brönsted's subsequent career, as he held the chair until his death 39 years later. His laboratory was at first in the Polytechnic Institute, and for a time facilities were very limited, as physical chemistry was a new subject and the laboratory had to be equipped from scratch. However, conditions gradually improved, and in 1919 he was relieved from the onerous task of teaching elementary inorganic chemistry. The greatest change in his working conditions resulted from his visit to the United States in 1926—27, when he was able to discuss the possibility of financing a new physicochemical laboratory in Copenhagen. The International Education Board finally met the cost of a new University Physicochemical Institute, which was completed in 1930. Here Brönsted had not only ideal working conditions, but also a delightful official residence where he and his family could exercise their hospitality and charm.

I shall now give some account of Brönsted's contributions to physical chemistry, not in strictly chronological order, but under their main headings.

The most important general interest in Brönsted's scientific work was undoubtedly thermodynamics. His earlier work dealt entirely with this topic, and even his later work on reaction kinetics has a strong thermodynamic flavour. His series of thirteen experimental papers on " Affinity " appeared during the years 1906—18, and constitute a veritable text-book of thermodynamics. Although Brönsted is well known for his later work on the thermodynamics of dilute electrolyte solutions, it is probably not generally realised how much he contributed to the fundamentals of chemical thermodynamics, where he can be ranked with Nernst and G. N. Lewis. At that time, although it was generally accepted that the affinity of a chemical process was measured by the maximum work and not by the heat of reaction, there were very few accurate or systematic measurements of affinity, and it was this gap which Brönsted set out to fill. In 1906 he showed how the heat and free energy changes in the interconversion of rhombic and monoclinic sulphur could be measured over a range of temperature, and he also speculated as to how affinity changes could be calculated from purely thermal quantities. It was of course Nernst, and not Brönsted, who first solved this last problem successfully, but Nernst himself acknowledged the importance of Brönsted's work in pointing the way. In a later paper in the same series (1910) Brönsted dealt with the thermodynamics of water–sulphuric acid mixtures, and gave one of the first correct treatments of the relations between the various differential and integral thermodynamic quantities in a mixture. In this paper he showed great ingenuity in combining vapour pressure, E.M.F., and calorimetric measurements, and (as in all these early papers) in obtaining accurate results with very modest resources.

Brönsted was always skilled at devising applications of E.M.F. measurements, and one example of this was his measurement of the free energy of formation of naphthalene picrate from its solid constituents, not at first sight a promising system for study by E.M.F. methods. Brönsted pointed out in 1911 that the free energy of this change was measured by the E.M.F. of the cell :

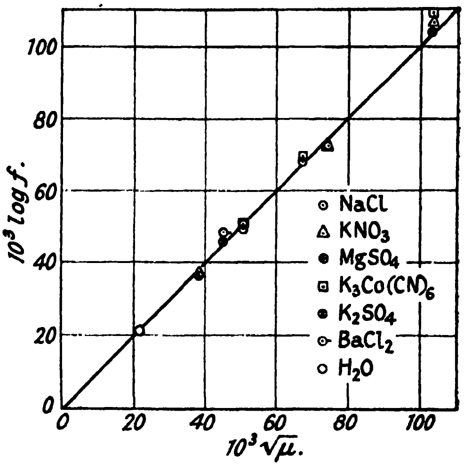
$$\text{Picrate electrode}|\text{solution I}|H_2Pt,\ PtH_2|\text{solution II}|\text{Picrate electrode}$$

where solution I is saturated with picric acid, and solution II with naphthalene + naphthalene picrate. Brönsted suggested using mercury–mercurous picrate for the picrate electrode, but was unable to make measurements on the above cell because the picrate solutions were reduced at the hydrogen electrodes. He was therefore compelled to use a very ingenious but laborious indirect method of measurement. It is interesting to note that in Oxford we have recently been able to measure the E.M.F. of the cell originally proposed by Brönsted by replacing the hydrogen electrodes by glass ones (which of course were not available to him) : the value obtained for the free energy of formation is exactly the same as that obtained in 1911 by the indirect method (Bell and Fendley, *Trans. Faraday Soc.*, 1949, **45**, 121).

Brönsted's thermodynamic studies soon led him into the field of electrolytes, first through E.M.F. measurements, and later through studies of solubility. It was becoming clear, partly through the work of Bjerrum, that very many electrolytes were completely dissociated in solution, and that their deviations from ideal thermodynamic behaviour could not be explained in terms of any association equilibrium. The concept of " activity " had been introduced by G. N. Lewis, and various authors had suggested that electrostatic forces between the ions might be of importance. Brönsted's approach was essentially an experimental one, and his solubility measurements became famous in 1924, when with LaMer he published data on activity coefficients of ions in very dilute salt solutions which provided a most striking confirmation of the theoretical treatment of Debye and Hückel, published while the work was in progress. It should, however, be stressed that this publication with LaMer was really the fifth of a series of papers on solubility, starting in 1919, interspersed with a number of other papers on the properties of ionic solutions. It is in fact remarkable how many important laws Brönsted was able to discover on the basis of his carefully designed and accurate experiments, in most cases before any theoretical basis for these laws was available. Thus he was able to show that the deviations of ionic solutions from ideal behaviour increase greatly with an increase in the charges on the ions present, and that in a solution containing several electrolytes the thermodynamic behaviour of a given ion is mainly a function of the ionic strength μ, defined as $\mu = \frac{1}{2}\Sigma m_i z_i^2$, where m_i is the concentration of an ion of charge z_i, and the summation extends over all the ions in the solution. In more concentrated solutions ions show individual properties not depending only on their charge, and Brönsted's " Principle of the specific interaction of ions " (1921) states that the individual properties of a given ion depend mainly on the ions of opposite charge which are present in solution. Brönsted's investigations on the effect of salts on ionic equilibria will be described under his kinetic work, but one simple principle is worth mentioning here : that even an ionic equilibrium will obey the classical law of mass action in presence of a large excess of non-participating salt. All these principles were later shown to have theoretical bases, and if we add to Brönsted's work the equally important investigations of his countryman Bejerrum, it will be seen that Denmark has had an altogether disproportionate share in the experimental foundations of the modern theory of electrolytes.

Most of Brönsted's solubility determinations, and many of his other researches, were carried out with the cobaltammines. These had been studied in great detail from the preparative point of view by S. M. Jörgensen, Brönsted's teacher, and he therefore had to hand large numbers of specimens and much information about these compounds. This was naturally a piece of good fortune, but Brönsted's genius lay in realising how admirably suited they were for his purposes. By suitable variations in the nature of the six groups co-ordinated to the central atom, ions can be produced with valencies varying from +3 to −3, and by combining these ions with one another or with other anions or cations it is possible to obtain salts of many charge-types and of widely varing solubility. Most of these salts are well-defined and crystalline, and they can be determined accurately even in very dilute solution by the simple process of treatment with sodium hydroxide and distillation of the ammonia into standard acid. These properties made them almost ideal for investigation of solubilities in salt solutions, but there was a great deal of ground-work to be done before the most suitable salts could be chosen : thus in his 1920 paper he measured the solubilities of 90 salts at two temperatures. The salts finally used by Brönsted and LaMer were the following :

FIG. 1.



The relation between the activity coefficient f *and the ionic strength* μ *for a uni-bivalent cobaltammine salt in the presence of solvent salts of various types. The heavy line represents the theoretical equation* — *log* $f = 1{\cdot}00\sqrt{\mu}$.

(*Reproduced by permission from* J. Amer. Chem. Soc., 1924, **46**, 568.)

$[Co(NH_3)_4C_2O_4]^+[Co(NH_3)_2(NO_2)_2C_2O_4]^-$ $s = 4{\cdot}9 \times 10^{-4}$
$[Co(NH_3)_4(NO_2)(CNS)]^+[Co(NH_3)_2(NO_2)_2C_2O_4]^-$ $s = 3{\cdot}3 \times 10^{-4}$
$[Co(NH_3)_4C_2O_4]_2^+[S_2O_6]^=$ $s = 1{\cdot}5 \times 10^{-4}$
$[Co(NH_3)_6]^{+++}[Co(NH_3)_2(NO_2)_2C_2O_4]_3^-$ $s = 5{\cdot}0 \times 10^{-5}$

The saturated solutions were obtained by the simple expedient of letting the solvent trickle slowly down a long vertical tube packed with crystals, a method which had been used by Brönsted much earlier in his measurements on rhombic and monoclinic sulphur. In spite of the low solubilities involved, an accuracy of about 0·3% was attained, as may be seen from Figure 1. The line drawn represents the predictions of the Debye–Hückel theory, which are clearly followed very closely.

The cobaltammines also played a considerable part in the development of Brönsted's ideas on acids and bases, and there is one other example of their use which may be mentioned here. On a simple electrostatic picture the solubility of a salt in different solvents should be a smooth function of the dielectric constant, but this is not so in practice, no doubt largely because of the part played by non-electrostatic factors. In a paper given to the 1931 meeting of the British Association Brönsted reported solubility measurements on the two substances $Co(NO_2)_3(NH_3)_3$ and $[Co(NO_2)_2(NH_3)_4]^+[Co(NO_2)_4(NH_3)_2]^-$ which contain exactly the same chemical groupings, but are respectively a non-electrolyte and a uni-univalent salt. By considering the ratio of the solubilities of these two substances, rather than the solubility itself, he hoped to eliminate the non-electrostatic factors, and he did in fact find a fairly regular behaviour for nine solvents with dielectric constants ranging from 21 to 84.

Apart from electrolytes, a particular thermodynamic problem which interested Brönsted from 1930 onwards is the effect of molecular size on thermodynamic properties. He carried out experiments on the solubilities and distribution between phases of molecules (or colloidal particles) which were chemically very similar, and differed mainly in size. These led him to the concept of an " isochemical series," and he established several laws governing the solubilities and other properties of such a series. Although he did not realise that large entropy effects might be present in mixtures of molecules of different sizes, Brönsted's laws are essentially the same as those developed recently for high polymers such as rubber. Some of Brönsted's last published work was on the vapour pressures of mixtures of the normal paraffins, for which he obtained experimental results of very high accuracy, and established some new regularities which have not yet been explained theoretically. This work contains some very neat experimental devices : for example, in order to weigh a vessel containing liquid and vapour without detaching it from the rest of the apparatus, he suspended it from an ordinary balance and used as a connecting tube such a fine glass capillary that it had little effect within the sensitivity of the balance.

Brönsted's work on isochemical series is of particular interest, because it represents one of the few cases in which he gave a molecular interpretation for the laws which he had established experimentally. In general he was curiously reluctant to consider any detailed molecular picture, preferring to derive from experiment empirical regularities which should be independent of any particular features of the molecules concerned. For example, one sometimes felt that he regretted the mechanistic explanation given by the Debye–Hückel theory for the laws which he had established experimentally, and other examples of a similar attitude will be given later. I well remember his indignation when I suggested to him, shortly before his death, that a statistical approach was helpful in explaining the laws of thermodynamics to students.

Certainly there was no suggestion of any molecular interpretation in his writings on the fundamental bases of thermodynamics, which occupied him to an increasing extent during the last ten years of his life. Although he criticised severely the conventional approach to the Second Law, his treatment remained a strictly phenomenological one. It is difficult to give an estimate of the value of this work, and I shall not attempt to summarise its content here. It roused violent controversy in Denmark, but has received little attention elsewhere : it is usually regarded as formally correct, but rather sterile. It is true that a similar view was at one time held about Brönsted's acid–base definition, which proved to have such a widespread importance, and it would indeed be interesting if his concepts of heat and entropy should eventually prove equally fruitful. They may perhaps be helpful in treating processes in which a steady state is set up by the irreversible flow of energy or matter through the system, a field which Brönsted had begun to study experimentally shortly before his death.

The second main field of Brönsted's activities was reaction kinetics, and in particular catalysis by acids and bases. This interest arose comparatively later in Brönsted's scientific development, but is probably the work for which he is best known, especially outside Denmark. It was closely connected with his work on electrolytes, and it is difficult to trace the exact order in which the various interwoven ideas arose, since papers on both kinetic and thermodynamic topics followed one another with bewildering rapidity in the nineteen-twenties.

Brönsted first used kinetic measurements in 1921 in connection with the effect of salts on acid–base equilibria. He was particularly concerned to show that the effect of salt concentrantion on hydrogen-ion concentration depends on the nature of the equilibrium involved : for example, in the system

$$CH_3{\cdot}CO{\cdot}OH \rightleftharpoons CH_3{\cdot}CO{\cdot}O^- + H^+$$

the hydrogen-ion concentration will be increased by added salt, while the equilibrium

$$NH_4^+ \rightleftharpoons NH_3 + H^+$$

will be little affected by salt additions, and in the system

$$[Fe(H_2O)_6]^{+++} \rightleftharpoons [Fe(H_2O)_5OH]^{++} + H^+$$

the hydrogen-ion concentration will be decreased by addition of salt. These results follow directly from the Debye–Hückel expression for activity coefficients, but were derived by Brönsted from the experimental evidence on the activity coefficients of ions of different charges. In order to test his conclusions it was necessary to measure the hydrogen-ion concentrations in these solutions, and for this purpose he used the rate of reaction of diazoacetic ester with water to give glycollic ester and nitrogen, a well-known example of hydrogen-ion catalysis. This at once raised questions of fundamental importance, for it was held in many quarters that the reaction velocity in such a system was proportional to the activity rather than to the concentration of hydrogen ions. Brönsted showed definitely that the concentration was the appropriate quantity : for example, when only a strong acid is present, the effect of added salt on the reaction velocity is much less than its effect on the hydrogen-ion activity. This justified the use of the diazoacetic ester reaction for measuring hydrogen-ion concentrations, and the salt effects observed with solutions of weak electrolytes agree with those predicted from activity data. This type of kinetic salt effect, depending on the displacement of an equilibrium, was termed by Brönsted a " secondary salt effect."

There existed at the time a mass of unco-ordinated data on the effect of added salts on reaction velocities, including many reactions involving only strong electrolytes, where no secondary salt effect could be involved. In this latter class of reaction it is customary to speak of " primary salt effects." Brönsted next showed in 1922 that all the existing data for primary salt effects could be summarised by the following simple statement : reactions between ions of like charge exhibit a large positive salt effect, reactions between ions of unlike charge a large negative salt effect, and reactions between an ion and a neutral molecule a small salt effect which may be either positive or negative. This classification was in itself a great step forward, but Brönsted gave it a further interpretation in terms of his famous expression for the effect of environment on the rate of a chemical reaction. For a reaction between two species A and B the expression for the reaction velocity v is

$$v = k[\mathrm{A}][\mathrm{B}]\frac{f_{\mathrm{A}}f_{\mathrm{B}}}{f_{\mathrm{X}}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k is independent of environment, f is an activity coefficient, and X represents the " critical complex " of A and B through which they must pass in order to react. It now seems obvious to us that the correct expression must involve the activity coefficient of some intermediate complex, as well as those of the reacting species, but Brönsted was the first to realise this, though the concept of a critical complex had previously been employed by Marcellin. We know very little about the nature of X, but we do know that its charge is the algebraic sum of the charges on A and B, and this is sufficient to predict approximately how its activity coefficient will vary with salt concentration. Nowadays this prediction would be made on the basis of the Debye–Hückel theory, but Brönsted again had to use the experimental data available for ionic activity coefficients, and was able to show that equation (1) corresponds to the rules for the salt effect given above, and agrees approximately with the magnitude of the observed effects. In particular it shows that in a reaction involving an ion and a neutral molecule (such as the decomposition of diazoacetic ester ion in presence of hydrogen ions) the activity coefficient factor will be near to unity, and hence the reaction velocity will be proportional to the concentrations of ester and hydrogen ions, and not to their activities. After the advent of the Debye–Hückel theory Brönsted made more measurements on salt effects in very dilute solutions, and found a complete confirmation of equation (1). It is interesting to note that Brönsted did not attempt to give any detailed molecular explanation of this equation, and the semi-thermodynamic derivation which he gave in 1922 was not made much clearer by a more detailed treatment in 1925. Brönsted's equation is now of course regarded as a special case of the transition-state expression for reaction velocity, but Brönsted himself showed little interest in later developments in this field.

The second major advance which served to clarify a large mass of kinetic work was Brönsted's extended definition of acids and bases, first published in 1923. Identically the same definition was put forward almost simultaneously by Lowry in this country. This definition is now generally accepted : it states that *an acid is a species which has a tendency to split off a proton, and a base is a species which has a tendency to add on a proton.* All acids and bases can therefore be arranged in conjugate or corresponding pairs according to the scheme

$$\mathrm{A} \rightleftharpoons \mathrm{B} + \mathrm{H}^+$$

This definition of acids includes not only uncharged molecules such as $CH_3{\cdot}CO_2H$, but also anions like HSO_4^-, $HPO_4^{=}$ and cations like NH_4^+, $[Fe(H_2O)_6]^{+++}$. The new definition of bases was even more fruitful, since there had previously been great confusion, for example as to whether the ammonia molecule or the hypothetical ammonium hydroxide should be regarded as a true base. The Brönsted–Lowry definition includes uncharged bases like NH_3, NMe_3 and anion bases such as $CH_3{\cdot}CO{\cdot}O^-$, OH^-, $CO_3^=$. It was not so easy to find an example of a cation base, but once again the cobaltammines and similar compounds came to the rescue: for example the ion $[Co(NH_3)_3(H_2O)_2OH]^{++}$ is a base in virtue of the reaction

$$\underset{\text{Base.}}{[Co(NH_3)_3(H_2O)_2OH]^{++}} + H^+ \longrightarrow \underset{\text{Acid.}}{[Co(NH_3)_3(H_2O)_3]^{+++}}$$

It is immediately clear that the hydroxyl ion is not in any way unique, since it is only one member of a whole class of anion bases. On the other hand the hydrogen ion does appear to occupy a privileged position as long as we write it as H^+, *i.e.*, a bare proton. However, following Fajans and others, Brönsted realised that the free proton could not exist in any significant concentration in the presence of other molecules, and that in aqueous solution it existed as the hydroxonium ion, H_3O^+, entirely analogous to the ammonium ion, NH_4^+. In fact, the "hydrogen ion" is a different entity in each solvent, in each case being only one of a class of cation bases.

Once the claim of hydrogen and hydroxyl ions to uniqueness has been abandoned, it becomes possible to write all the reactions of acids and bases (variously described as dissociations, neutralisations, hydrolyses, buffer systems, etc.) in the symmetrical form:

$$\text{Acid (1)} + \text{Base (2)} \rightleftharpoons \text{Base (1)} + \text{Acid (2)}$$

Some examples of this are given in the following table, and a similar set could be given for non-aqueous solvents.

A_1 +	B_2 ⇌	A_2 +	B_1	Description.
$CH_3{\cdot}CO_2H$	H_2O	H_3O^+	$CH_3{\cdot}CO{\cdot}O^-$	Dissociation in water *or* buffer action in acetic acid + acetate.
$CH_3{\cdot}CO_2H$	NH_3	NH_4^+	$CH_3{\cdot}CO{\cdot}O^-$	Dissociation of acetic acid in liquid ammonia, *or* dissociation of ammonia in glacial acetic acid, *or* neutralisation of $CH_3{\cdot}CO_2H$ by NH_3, with or without solvent.
H_2O	$CH_3{\cdot}CO{\cdot}O^-$	$CH_3{\cdot}CO_2H$	OH^-	Hydrolysis of acetate solutions.
NH_4^+	H_2O	H_3O^+	NH_3	Hydrolysis of ammonium salts, *or* buffer action in NH_3 + NH_4Cl.
H_2O	$HPO_4^=$	$H_2PO_4^-$	OH^-	Hydrolysis of secondary phosphates.
H_2O	NH_3	NH_4^+	OH^-	Dissociation of ammonia in water.
$H_2PO_4^-$	H_2O	H_3O^+	$HPO_4^=$	Dissociation of primary phosphate *or* buffer action in mixtures of primary and secondary phosphate.

Since the hydrogen and hydroxyl ions are not unique among acids and bases, there is no reason why they should have the monopoly of catalytic cation in chemical reactions, and Brönsted's next important contribution was the experimental demonstration of *general acid–base catalysis* in a number of reactions. Brönsted and Pedersen's paper on the nitroamide decomposition, published in 1924, showed that the reaction was catalysed by the following classes of base:

(1) Anion bases like acetate ion, oxalate ion, etc.
(2) Uncharged bases like aniline and pyridine.
(3) Cation bases like $[Co(NH_3)_5OH]^{++}$.

Brönsted and Pedersen made a detailed study of catalysis by anion bases, and later papers (1925—34) extended this to the other types of base and also to non-aqueous solvents. The mutarotation of glucose offered rather more complications, since it is catalysed by both acids and bases. Thus in an acetate buffer solution the full expression for the reaction velocity is

$$v = k_0 + k_1[H_3O^+] + k_2[OH^-] + k_3[HOAc] + k_4[OAc^-]$$

However, by carefully designed experiments it was possible to separate out the effects of different species, and the 1927 paper by Brönsted and Guggenheim demonstrated the catalytic effect of anion bases, uncharged bases, cation bases, uncharged acids like acetic acid, and cation acids like the ammonium ion. Very similar conclusions were published by Lowry in the same year, though his investigations were less complete.

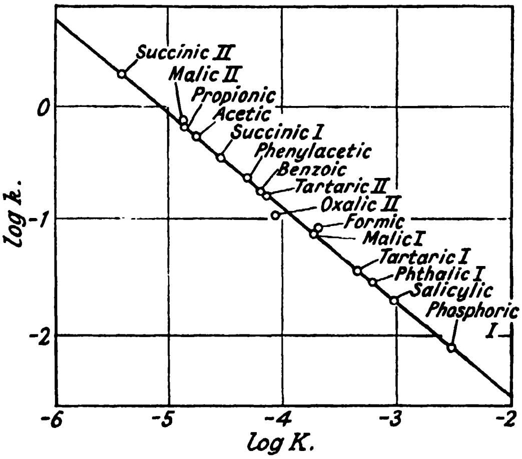
The idea of catalysis by species other than hydrogen and hydroxyl ions was not altogether a new one, and in particular the "dual theory," suggested by Acree, Snethlage, and H. S. Taylor, had assumed catalysis by undissociated acid molecules. However, most of their deductions were based upon incorrect values for the degree of dissociation of electrolytes, and did not allow for primary and secondary salt effects. In his monograph on "acid-base catalysis" (published in Danish in 1926, English translation in 1928) Brönsted devoted a good deal of space to a severe criticism of this earlier work, and was in fact able to show that in almost all cases the supposed catalytic effect of acid molecules was based on a misinterpretation of the data, or could reasonably be attributed to a salt-effect. The only notable exception to this statement was Dawson's work on the acetone–iodine reaction, and here Brönsted's strictures were rather less than just. It is true that Dawson did not take into account recent views on electrolytes and that his experiments were planned in such a way as to involve complicated salt-effects. Nevertheless, there is no doubt that his work definitely establishes catalysis by carboxylic acid molecules, and in fact still provides the most extensive set of data for this type of catalyst, although his numerical values need some revision in the light of modern developments.

If we consider a series of similar acids and bases, it is natural to expect that their catalytic power for a given reaction will depend on their acidic or basic strength. In his first paper on the nitroamide decomposition Brönsted gave a quantitative form for this dependence which has been found to be generally valid, and which is commonly known as the "Brönsted relation." For basic catalysis it can be written in the form :

$$k_b = GK_b^{\alpha}$$

where k_b is the catalytic coefficient of a base of dissociation constant K_b, and G and α are constants characteristic of the reaction, the temperature, and the solvent, α being less than unity. Figure 2 shows how well this relation is obeyed for the anion-catalysed decomposition of nitroamide: for most other reactions the agreement is rather less good. As in many other cases Brönsted arrived at the form of this relation primarily by considering the experimental data. The only theoretical basis which he gave for it was a vague and unsatisfactory one, and he was not particularly interested in later attempts to interpret the relation in terms of molecular potential-energy curves.

FIG. 2.



The relation between catalytic effect and acid–base strength for the anion-catalysed decomposition of nitramide.

(*Reproduced by permission from* Z. physikal. Chem., 1924, **108**, 210.)

I must now attempt some kind of summing up of Brönsted as a scientist and as a man. His skill as an experimentalist was not immediately apparent because of the simple nature of many of his methods, and it took some time to realise how much skill and discrimination lay behind an apparently simple piece of experimental work. His great strength lay in the choice of the most suitable substance or reaction, and in the planning of a series of experiments to attain the desired end with the greatest certainty and economy. For this reason his researches always had a much wider application than the immediate purpose in hand, and one of the greatest benefits of working with him was the opportunity of sharing his insight into general methods and planning of research. Many of his pupils have modelled their subsequent work on Brönsted's prototypes : for example, most later work on activity coefficients from solubility measurements and on general acid–base catalysis follows closely on some lead originally given by Brönsted.

It is more difficult to place Brönsted as a theoretical physical chemist in relation to the main developments of his time. We have already seen several examples of his absorption in thermodynamics and his love of an experimental approach, and the adjective "classical" seems an appropriate one to describe his contributions to physical chemistry. In the field of solutions his work has had a clarifying effect to which it is difficult to find a parallel. Although his mind was a most agile one, several of the major trends in modern physical chemistry failed to rouse his interest : for example, the experimental and theoretical study of molecular structure, and the theoretical treatment of reaction velocities. Looking back, it seems strange that one of the greatest investigators of reaction kinetics in solution should never have deliberately measured an activation energy. On the other hand, there is no doubt that this limitation of interest enabled him to attack his chosen field with greater intensity and singleness of vision.

Brönsted was an individualist in his work, and owed little to the influence of other scientists, though the tradition of Julius Thomsen fostered his early interest in thermodynamics, and his training under S. M. Jörgensen introduced him to the cobaltammines and gave him high standards of preparative and quantitative work. There is only one instance where he collaborated with another scientist outside his own field, and that was in his famous work with Hevesy on the separation of the isotopes of mercury and chlorine by ideal distillation at low pressures. In his earlier days he had few junior collaborators, but in the period 1922—37 many chemists from other countries, particularly England and the United States, went to work with him. I myself spent four years in his laboratory, and I remember very clearly the impression of integrity and intensity of scientific endeavour which I received. One guest worker described his laboratory as a place of " high chemical potential," and the phrase does give something of the tense and personal feeling which Brönsted inspired. He showed great kindness and consideration to his collaborators from overseas, and the subsequent work done by many of them shows the lasting effect of his influence. On first acquaintance he seemed rather reserved, but one soon realised that this arose from an unwillingness to talk carelessly or lightly on scientific matters. When he had once embarked on a discussion his acuteness and remorseless logic were remarkable, and there can be very few occasions on which he was worsted in a scientific argument. He did in fact very much enjoy a keen polemical discussion, and never hesitated to express his criticisms in an edged and sometimes personal manner. This involved him in a number of controversies, beginning in 1908 with his criticism of Nernst's concept of " ideal concentrated solutions," and ending with a lengthy argument with Danish physicists about the foundations of thermodynamics.

Brönsted's duties as a professor involved a considerable amount of elementary teaching, especially in his earlier days, and his lectures were elegant in delivery and content. Their concentrated exactness made them perhaps rather indigestible for the average student, and the same was true of his text-book of physical chemistry. The later editions of this book incorporated his own treatment of thermodynamic principles, and we can sympathise with the polytechnic student who had to use terms like " heat " and " work " in one sense in his physics and engineering, and in another sense in his chemistry. The Danish system involves a large amount of oral examination, and in his earlier days Brönsted gained some reputation for severity as an examiner: his standards were certainly high, and he was not much given to compromise, least of all in scientific matters. There are many anecdotes about these examinations, and I remember one candidate who had rashly professed some knowledge of the occurrence and properties of the silicates, and who was finally driven by Brönsted's remorseless logic into maintaining that a paving-stone would probably dissolve completely if stirred up with a little water! However, as he became older Brönsted became more lenient towards his younger students, though he could still be a formidable opponent to candidates for the doctorate degree.

In private life Brönsted had great personal charm and a wealth of interests outside his science. The chief of those was his love of the countryside and its people, which remained with him all his life. His family holidays were usually spent in some remote part of the country, and he had a very extensive knowledge of Danish wild life, especially of birds. It is interesting to note that his last publication, just before his death, was a note describing some observations on insect behaviour made during his summer holiday. He felt very keenly about the preservation of natural beauty and nature reserves, and took a prominent part in campaigns to this end. Music and painting were also among his accomplishments, and through his marriage he came into close contact with many of Denmark's leading artists and musicians. He had a wide knowledge of literature in several languages and a remarkable gift not only for accuracy but also for elegance in expression in both Danish and English.

Brönsted travelled widely in Europe, and made several visits to the United States. In spite of his strong Danish patriotism he had a great deal of sympathy and understanding for other countries, and especially for England. His early contacts were mostly with German scientists, but after the First World War his sympathies turned decisively towards this country. In 1920 he spent several months in England, mainly with Professor Donnan at University College, and he made at least seven more visits before 1939, including several to attend meetings of the Faraday Society. Among many other honours he was made an honorary member of the Academy of Arts and Sciences in 1929, an honorary Fellow of the Chemical Society in 1935, and an honorary doctor of London University in 1947.

The Second World War served only to strengthen the ties which bound him to English things and English people, and he never had any doubts as to the rightness or the eventual outcome of the struggle. From the first day of the German occupation he spent several hours daily listening to the broadcast news from London, and he also read widely in English history and biography: when I visited him in 1945 he still had on his table a list of English Foreign Secretaries from 1769 onwards. The occupation also turned his attention to public affairs in general, in particular the vexed question of Schleswig and the Danish–German frontier, about which he spoke and wrote in his usual forthright manner. Nevertheless, it was a surprise to many of his friends when in 1947 he accepted nomination as a candidate for the Danish parliament, and a still greater one when on October 28th he was elected. He took this responsibility seriously, and immediately began to study parliamentary procedure, but he was overtaken by his last fatal illness before he could take his seat, and died on December 17th. It is interesting to speculate how he would have fared in Parliament and how his logical and uncompromising mind would have dealt with the half-truths of politics. He himself believed that many of the ills of mankind were due to the lack of logic and precise definition in public affairs, and it is an open question whether the application of this principle would have brought success or frustration.

It is very fortunate that Brönsted was able to visit England again in the summer of 1947, when he attended the Chemical Society Centenary celebrations and the International Congress. He enjoyed this visit to the full: not only the formal scientific occasions, but also the quieter times which he and Mrs. Brönsted spent in the homes of their English friends, and by themselves in a remote corner of the English countryside. It was a great shock to hear of his sudden death so soon afterwards, and many people in many countries will mourn him, not only because of his contributions to science or for his inspiring personal genius, but also as a fine and lovable person. Many of his ideas have passed into the common currency of physical chemistry, and, although one hesitates to predict the future of any scientific subject, it is difficult to imagine a state of affairs in which they would not still be valid and useful. This society has done itself a great honour by numbering him among its Honorary Fellows.

R. P. BELL.

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Newer Developments of the Chemistry of Many-membered Ring Compounds.

CENTENARY LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY IN LONDON ON FEBRUARY 17TH, 1949.

By V. PRELOG.

I AM able to speak about the newer developments of the chemistry of macrocyclic compounds thanks to the fortunate circumstance that I am working in the Laboratory of organic chemistry at the Institute of Technology in Zürich. In this laboratory the many-membered rings were discovered by L. Ruzicka and the fundamental analytical and synthetical work has been done on this interesting group of compounds. Ruzicka himself lectured on his work before the Chemical Society in London almost exactly 15 years ago.[1] The most important theoretical consequences of these investigations and especially their influence on the so-called strain theory form part of general text-book chemistry to-day. Moreover, the perfume industry could not dispense with the artificial musk-like scents, which became available through this work.

In spite of the wide extent of this field only few laboratories have devoted themselves to the chemistry of many-membered ring compounds. I would like to mention, in addition to the Zürich Laboratory and a connected group led by M. Stoll in Geneva, Carothers, Adams, and Blomquist in America, and Ziegler, Lüttringhaus, and Hunsdiecker in Germany. If I concern myself mostly with the newer work of our own group, it is only on account of restricted time.[2] For the same reason I cannot deal now with the very interesting recent work on many-membered ring peptides, antibiotics, and alkaloids.

The reason why the chemistry of many-membered ring compounds was not more intensively studied lay in their difficult accessibility. In the heroic age, Ruzicka and his co-workers prepared the many-membered ring ketones, which they used as starting materials for other compounds of this group, by dry distillation of the rare-earth salts of dicarboxylic acids.[3] In favourable cases the yields reached a few per cent. The introduction of the dilution principle by K. Ziegler, H. Eberle, and H. Ohlinger[4] did not make the many-membered ring derivatives readily available, since the technique of ring-closure in great dilution is rarely simple. All general procedures for the preparation of macrocyclic compounds had still another important disadvantage. The compounds of medium ring-size, containing 8 to 12 members, could be prepared only in disappointingly low yields of a few tenths per cent.

The introduction of the very advantageous acyloin synthesis,[5] which allows preparation in very good yields of ring compounds having more than 8 members, formed therefore a starting point for new approaches to this field. This synthesis leads from easily accessible dicarboxylic acid esters in a simple way without using great dilutions to macrocyclic acyloins, which can be converted easily into various other cyclic compounds. The following formulæ show a variety of reactions, which were carried out recently:

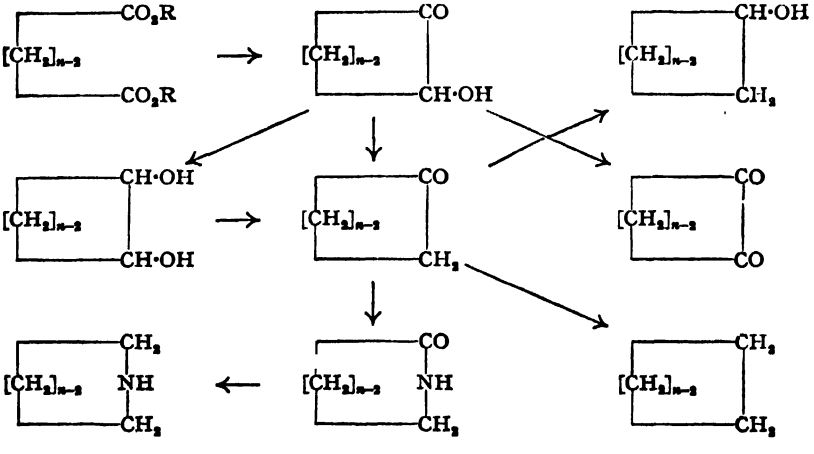
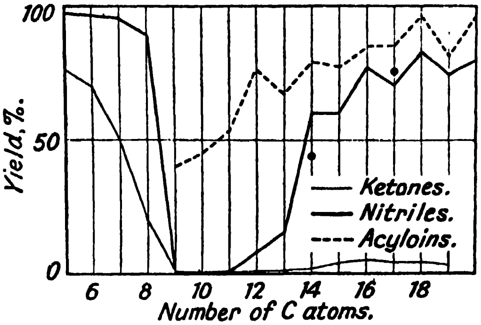


Fig. 1 illustrates the dependence of yield on ring size for the three most important general procedures for the preparation of many-membered ring compounds: the preparation of ring ketones according to Ruzicka, the preparation of imino-nitriles by Ziegler's method, and the acyloin procedure. One can see that it is now possible to obtain ring-compounds of every size in reasonable yield. In this way the field of many-membered ring-compounds became a real playground for the organic chemist. The acyloin procedure leads to the democratisation of this hitherto very aristocratic group of compounds. It is now no more difficult to obtain *cyclo*decanone than any higher aliphatic ketone.

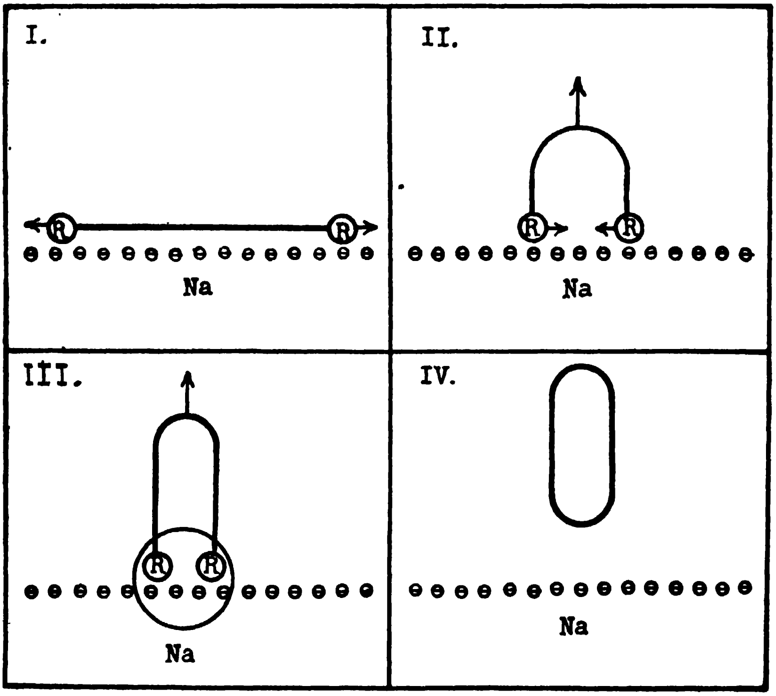
A very elegant application of the acyloin synthesis to a macrocyclic compound is exemplified in the synthesis of civetone by M. Stoll, J. Hulstkamp, and A. Rouvé.[6] It was possible to synthesise both *cis*- and *trans*-isomers of civetone and this is the first case of a double bond incorporated in a ring in both *cis*- and *trans*-configuration in known fashion.

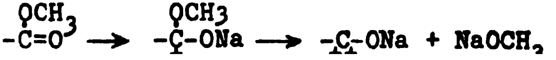
FIG. 1.



The problem of the surprisingly good yields of many-membered ring acyloins obtained from the acyloin synthesis in concentrated solutions is explained by our reaction mechanism shown schematically in Fig. 2.[7] The two electrophilic carbon atoms at the ends of the chain of a dicarboxylic acid ester are first adsorbed by the electron-covered surface of the molten sodium. So far as the flexibility of the carbon chain allows, the electrophilic residues can slide over the metal surface and can thus approach each other. As less energy is necessary for this than for splitting the molecule off the surface, the collisions of the adsorbed molecule with other molecules lead to the approach of the terminal carbon atoms and finally to the ring closure. After the ring closure the molecule no longer possesses electrophilic centres and is therefore no longer bound to the surface.

FIG. 2.





$$\overset{\text{OCH}_3}{-\text{C}=\text{O}} \longrightarrow \overset{\text{OCH}_3}{-\text{C}-\text{ONa}} \longrightarrow -\text{C}-\text{ONa} + \text{NaOCH}_3$$

The work on many-membered rings was from the beginning carried out with two motives, the one practical—the preparation of musk-like perfumes—and the other theoretical—the investigation of the influence of ring size on the physical and chemical properties. It seemed that this second aim would not have much interest since according to older views the higher unstrained ring homologues of *cyclo*hexane should not differ from it more than the higher aliphatic homologues differ from the lower. In fact *the physical and the chemical properties of the many-membered ring compounds do show a peculiar and unexpected dependence on ring size.*

FIG. 3.

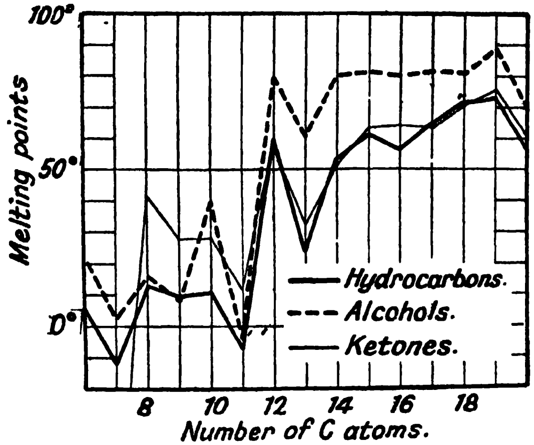
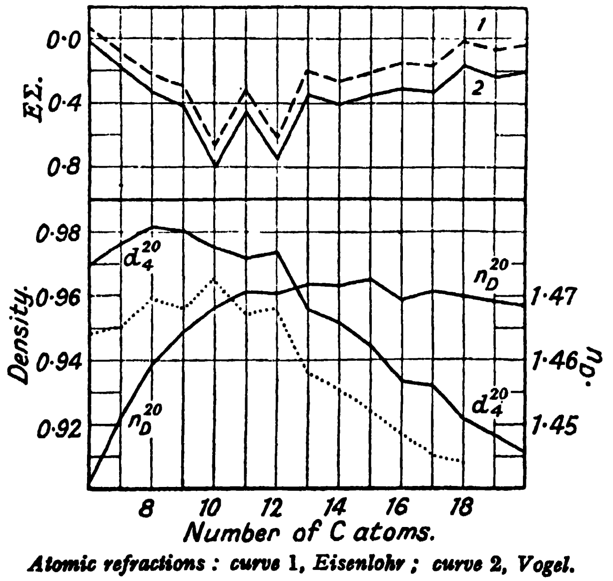


Fig. 3 shows, for example, that the curves of melting point against ring size do not rise steadily as with aliphatic homologues.[8] As no simple explanation of these curves is possible we shall turn rather to consideration of those more readily explicable properties which are not dependent on lattice forces. Such, for example, are the density and the molecular refraction in the liquid state. Most of the investigated series of alicyclic many-membered ring compounds show a maximum of density and a depression of molecular refraction at medium ring size. In this manner they differ from the aliphatic homologous series, which show a steady increase or decrease of density and no appreciable deviation $E\Sigma$ from the calculated molecular refraction.

FIG. 4.

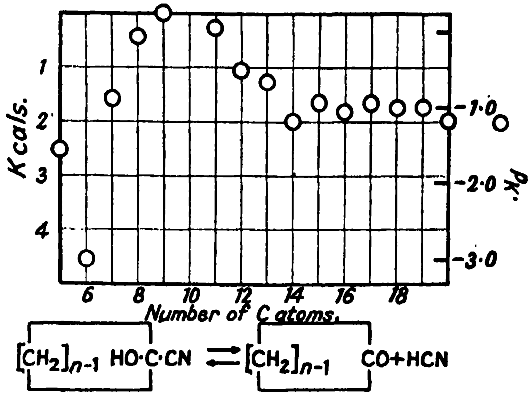


Atomic refractions: curve 1, *Eisenlohr; curve* 2, *Vogel.*

Fig. 4 describes the above-mentioned properties as a function of ring size in the series of cyclanol acetates.[8] Cyclanol acetates are specially suitable for such measurements, because the whole series is liquid at room temperature so that no corrections are necessary.

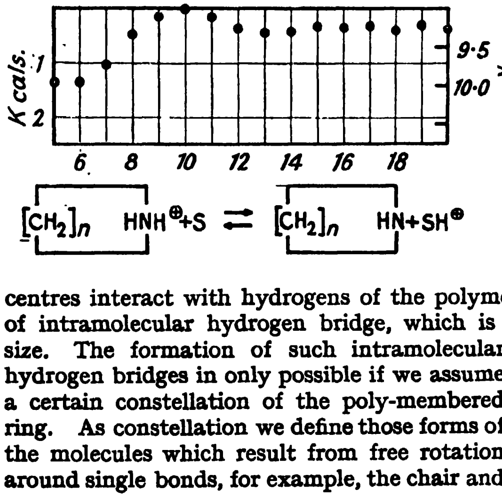
To the extreme values of the physical properties correspond extreme values of the chemical properties of the medium-size ring compounds. As the first example of the chemical properties, the dependence of the equilibrium constants on ring size is shown in Fig. 5 for the reaction between cyclanones and hydrogen cyanide in alcoholic solution.[9] The negative logarithms of the dissociation constants and the free energy of the reaction are plotted against ring size, the influence of which is unexpectedly great. The two extreme values lie on the limits of possible experimental determination. That means that *cyclo*hexanone cyanohydrin scarcely dissociates at all, whereas *cyclo*decanone does not add on hydrogen cyanide. For comparison, the dissociation constant for dioctyl ketone cyanohydrin is given on the right-hand side of the graph.

Fig. 5.



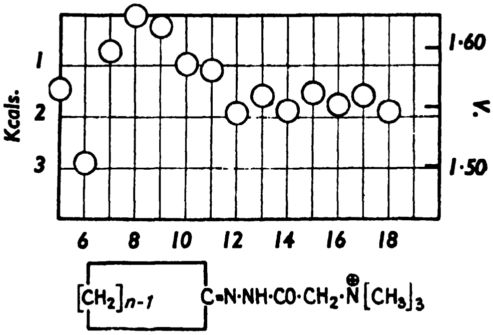
As a further example of the dependence of an equilibrium constant on the ring size we can consider the dissociation constants of polymethylene-imines shown in Fig. 6.[10] We also measured polarographically the half-wave potentials for the cathodic reduction of the Girard-T derivatives of cyclic ketones, which are shown on Fig. 7.[11] In spite of the fact that it is not a reversible reaction, we obtained a shape of curve which shows a dependence of half-wave potentials on ring size very similar to those in the two foregoing examples.

Fig. 6.



The common feature in all these reactions is that at medium-ring size that reaction component is stabilised which contains a more nucleophilic oxygen or nitrogen: for example, ketone is stabilised with respect to cyanohydrin, imine with respect to the corresponding ammonium salt, hydrazone with respect to the reduced form. One possible explanation for this fact is that the nucleophilic centres interact with hydrogens of the polymethylene chain through formation of some kind of intramolecular hydrogen bridge, which is particularly strong if the ring has a medium size. The formation of such intramolecular hydrogen bridges in only possible if we assume a certain constellation of the poly-membered ring. As constellation we define those forms of the molecules which result from free rotation around single bonds, for example, the chair and the boat form of *cyclo*hexane. With respect to stability of form, the poly-membered rings stand in between the rigid small rings and the mobile aliphatic open chains, and therefore these compounds provide an interesting material for studies of the influence of constellation on chemical and physical properties. The following two factors will determine mainly the energy and the probability of a constellation: first, the van der Waals radii of the atoms, which are well illustrated by Stuart models, and secondly, such interactions as are not shown by atomic models—that is, forces not expressed in classical formulæ, for instance, those which restrict rotation around a single bond in aliphatic compounds in contradiction to the views of classical stereochemistry.[12] These forces cause the inequality

Fig. 7.



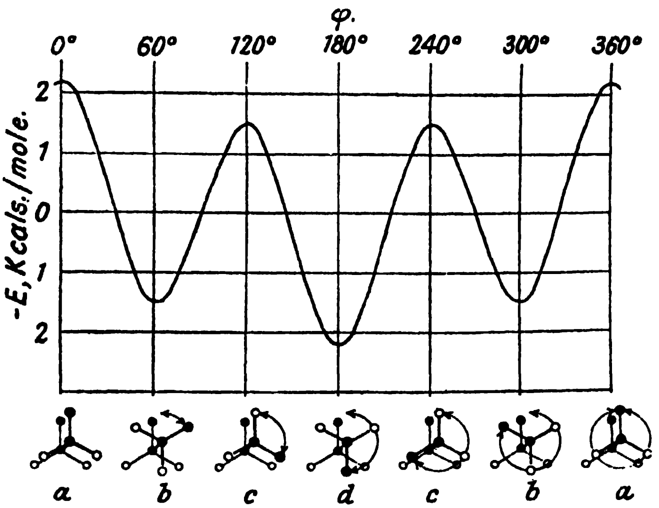
of various constellations of a polymethylene chain from the energetics standpoint. The changes of the potential energy of a chain of four methylene groups around the central C–C bond can be described approximately by the formula [13]

$$E = -1{\cdot}7\cos\phi - 0{\cdot}5\cos\phi \text{ kcals. per mole.}$$

This function is shown together with corresponding configurations in Fig. 8.

Two constellations *b* and *d*, which are separated from each other by energy barriers, are especially favoured. In a normal paraffin hydrocarbon the constellation *d*, which corresponds to the zigzag form of the chain, predominates. In *cyclo*-paraffins the polymethylene chain deviates the more from the constellation *d* the smaller the ring. In *cyclo*pentane and its lower ring homologues the chain is forced by ring strain into the energetically unfavourable constellation *a*. *cyclo*Pentane itself has, according to K. S. Pitzer,[14] a non-planar form because the deformation of the tetrahedral valency angles of the non-planar form is less serious than the unfavourable constellation of the planar form. From this it is understandable that the chair form, which is built from 6 energetically favourable constellations, predominates in *cyclo*hexane over the boat form, in which constellation *b* occurs 4 times and the unfavourable constellation *a* twice.

FIG. 8.



These considerations being transferred to homologous *cyclo*-paraffins and simultaneous account being taken of van der Waals radii, one has the interesting result that medium-sized rings with 8—12 members can only be built from less favourable constellations. In contrast to this, the chains of the higher *cyclo*-paraffins can again be constructed from energetically favourable constellations *b* and *d*. Just as in small rings classical strain and constellation work against each other, so in medium-sized rings van der Waals repulsive forces and constellation are opposed. The medium-sized rings suffer a greater interaction between atoms than in *cyclo*hexane : they are therefore at a higher energy level than unbranched aliphatic compounds.

Maxima and minima in the physical properties of medium-sized ring compounds may be explained in this way, for example, the reduction of electron polarisability and consequently of molecular refraction by the stronger interaction of non-adjacent atoms in the medium-sized rings.

In considering the influence of ring size on the chemical properties, for example, on the dissociation constants of the cyanohydrins, it should be realised that in small-ring ketones the oxygen stands outside the ring. In medium-sized rings we have many possible forms in between the two extreme constellations, which may be termed " O-outside " and " O-inside." Figs. 9 and 10 show such extreme constellations for *cyclo*decanone. The O-outside constellation of medium-sized ring ketones are marked out, first, by a more favourable constellation of the polymethylene chain,* and secondly, by an intramolecular interaction between the carbonyl

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* In the model shown by Fig. 9 we have 6 times the unfavourable constellation *c* and twice the favourable constellation *b*. If the oxygen atom is outside the ring, as in the model shown by Fig. 10, the unfavourable constellation *c* occurs 8 times.

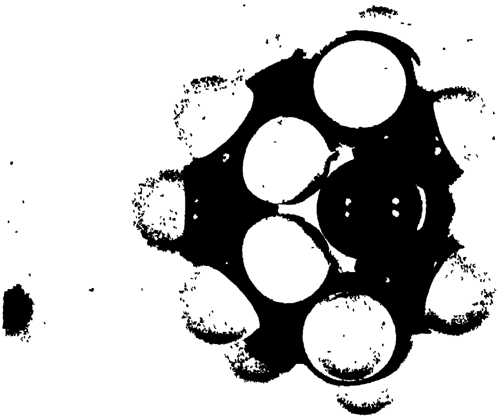


FIG. 9.

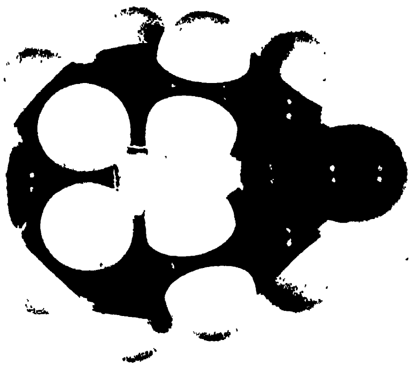


FIG. 10.

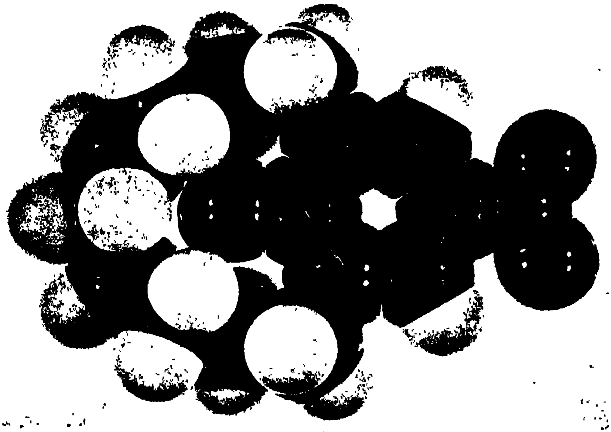


FIG. 11.

[*To face p.* 424.

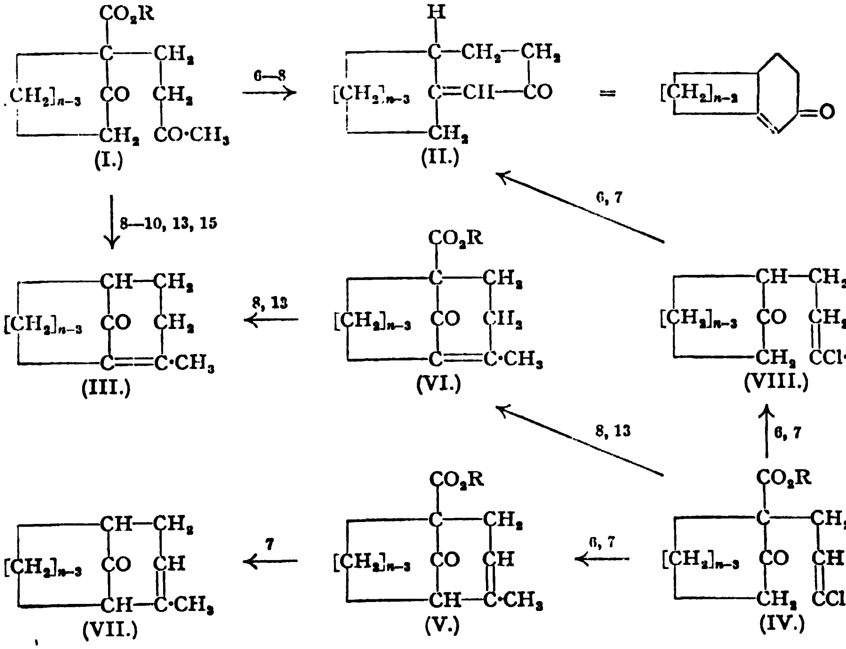
oxygen and the hydrogens of the polymethylene chain; the distance between these atoms is especially small in medium-sized ring ketones. The interaction is stronger in the ketone than in the cyanohydrin and stabilises the former, as was found experimentally. Very similar considerations can be developed for the other reactions mentioned.

In an attempt to prove the consequences of the " O-inside " configuration of cyclanones, Dr. Günthard studied the infra-red absorption spectra. As expected, the frequency of C=O bond-stretching band was smaller with a medium-ring ketone than in *cyclo*hexanone or a large-ring ketone. The following values (in cm.$^{-1}$) were obtained in the liquid state: *cyclo*hexanone 1710, *cyclo*octanone 1692, *cyclo*nonanone 1698, *cyclo*decanone 1694, *cyclo*undecanone 1700, *cyclo*dodecanone 1697, *cyclo*tridecanone 1707.*

In addition to the physical and physicochemical methods of approach, we tried to examine the question of the constellation of many-membered ring compounds by the classical methods of organic chemistry. Assuming that the rate of ring closure is influenced by constellation, it should be possible under favourable conditions to obtain information about the constellation of a monocyclic compound by transforming it into a bicyclic compound. We carried out a series of such experiments and found some facts which deserve brief mention.

Robinson and his co-workers [15] showed that condensation of the *cyclo*hexanonecarboxylic esters with quaternary bases of dimethylaminobutanone (" Mannich base ") gives compounds, which can be simultaneously saponified, decarboxylated, and cyclised to αβ-unsaturated octalones. We obtained analogous products (II) by condensing the cyclic β-keto-carboxylic esters (I) containing a 7- or an 8-membered ring.[16] In the case of the 8-membered ring we isolated a second isomeric αβ-unsaturated ketone (III), in which the carbonyl of the side chain had condensed with the active methylene group in the ring. The two isomers could be separated easily by making use of the fact that the second of them does not give the carbonyl group reactions, for example, does not react with Girard reagent-T. Ultra-violet absorption spectra and Kuhn–Roth oxidation provide evidence for the constitution. The compound with the bicyclic system condensed in the 1 : 2-position has an absorption maximum at a shorter wave-length and gives no acetic acid by oxidation, whereas the isomer with the bicyclic system condensed in the 1 : 3-position gives one molecule of acetic acid by oxidation and absorbs at longer wave-length. Using higher homologues of *cyclo*octanonecarboxylic ester, we got only products of the type (III)

Bredt's Rule.



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* Dr. G. B. B. M. Sutherland, Cambridge, who independently investigated the infra-red spectra of some cyclanones observed in *cyclo*octanone changes in the frequences of the C=O band at about 5·7 μ. as well as of the C–H band at about 1·75 μ., which indicate an intramolecular hydrogen bond.

These experiments permit some definition of the limits of validity of Bredt's rule, which states that in bridged-ring systems a double bond cannot start from a bridgehead. Fundamentally, Bredt's rule expresses the requirement of effective overlap of the *p*-electron orbitals constituting the π-electron orbitals of the double bond. Twisting of the inter-atomic axis in a bridged-ring system is thus the simplest case of that steric hindrance of π-electron resonance which has recently been much investigated in systems containing several conjugated double bonds. Bredt's rule is formally broken by the products (III) of the Robinson reaction containing a 1 : 3-bicyclic system, and it is therefore clear that a double bond may lie at the bridgehead of a bicyclic system if the ring only be large enough.

We investigated this problem more thoroughly by a variant of Robinson's synthesis.[17] We condensed the cyclanone carboxylic esters with γ-chlorocrotyl chloride (1 : 3-dichlorobut-2-ene) instead of with the quaternary salt of the " Mannich-base " and treated the products (IV) with concentrated sulphuric acid according to O. Wichterle.[18] The γ-chlorocrotyl derivatives give under these conditions γ-keto-butyl derivatives, which react further as in Robinson's synthesis but without saponification and decarboxylation. The carbonyl of the β-keto-carboxylic ester is less reactive than in ketones, and only bicyclic compounds condensed in the 1 : 3 position are formed independently of ring size. The compounds (V) from the starting material with 6- or 7-membered rings contain, however, no $\alpha\beta$-unsaturated carbonyl, as shown by ultra-violet absorption spectra, or in other words they obey Bredt's rule. In contrast, the compounds (VI) with 8-membered and higher ring are $\alpha\beta$-unsaturated ketones. Thus the limit of applicability of Bredt's rule lies between the systems with a 7- and an 8-membered ring.

The bicyclic α-keto-carboxylic acids (V) and (VI), which are obtained by the variant of the Robinson synthesis, show an interesting behaviour on decarboxylation. The compound (V) with two 6-membered rings cannot be decarboxylated even under drastic conditions. Similar examples are known from terpene chemistry, for example, camphoronic acid. On the other hand, the analogous acids, (V) with a 7- and (VI) with an 8-membered ring, decarboxylate easily at 240°, whereas the acid (VI) with a 13-membered ring decarboxylates even during the alkaline saponification of the ester. If we assume that an anion at the bridgehead is an intermediate, which must be stabilised by resonance with the carbonyl for the activation energy to be sufficiently low, then we can use these results as a contribution to the knowledge of the validity of Bredt's rule.

I should like to mention that γ-chlorocrotyl carboxylic esters (IV) can be saponified and simultaneously decarboxylated with a mixture of hydrochloric and acetic acids and that treatment of the resulting α-chlorocrotyl ketones (VIII) with sulphuric acid gives the same products (II) as the Robinson synthesis.

Since all experiments showed that the carbonyl in poly-membered ring compounds is feebly reactive, whereas the α-methylene groups are strongly reactive, we tried to condense cyclic ketones with nitromalonic dialdehyde (IX), which gives substituted *p*-nitrophenols easily with aliphatic ketones as was shown by Hill and by Kenner.[19] In fact, the many-membered ring ketones with a more than 8-membered ring gave compounds of the expected formulæ.[20] However, the influence of ring size on the formation of the bicyclic system showed an interesting effect. With 10- and higher-membered ring ketones yellow *p*-nitrophenoxides (XI) were directly obtained, which yielded on acidification *p*-nitrophenols (XII). Ketones with an 8- and a 9-membered ring gave instead colourless condensation products, which contained one molecule of water more than the expected *p*-nitrophenoxides. These products differ in their absorption spectrum from the *p*-nitrophenoxides and probably have the constitution (X).[21] On acidification, the product with a 9-membered ring gives immediately the corresponding *p*-nitrophenol, which can be converted by alkali into the normal *p*-nitrophenoxide. In contrast to this, the primary condensation product which contains an 8-membered ring gives on acidification a compound (XIII) which is tautomeric with the expected *p*-nitrophenol, as could be shown by a thorough investigation. This compound is converted by alkali back into the colourless salt (X), which contains 1 molecule of water more than the *p*-nitrophenoxide. We have here an interesting case of a compound in which the ring strain has overcome the tendency to form an aromatic system. This is in accordance with the model, which shows that the compound (XIII) is much less strained than the *m*-bridged benzene derivative. The *m*-bridged *p*-nitrophenols can serve as starting material for other series of *m*-bridged benzene derivatives, for example, 4-aminophenols (XIV), *p*-benzoquinones (XV), and quinols (XVI).[22]

In the above mentioned *m*-bridged bicyclic compounds the many-membered rings have forms which are very similar to the forms of monocyclic ketones with " O-inside " constellations : this can be seen from the model of a *m*-bridged *p*-nitrophenol, as shown in Fig. 11. Therefore it was interesting to test whether the influence of the medium-sized rings on the chemical properties of the bicyclic compounds was the same as in the monocyclic compounds. The aromatic part of the molecule served in these cases as a kind of indicator for the forces inside the ring.

m-*Bridged Benzene Derivatives.*

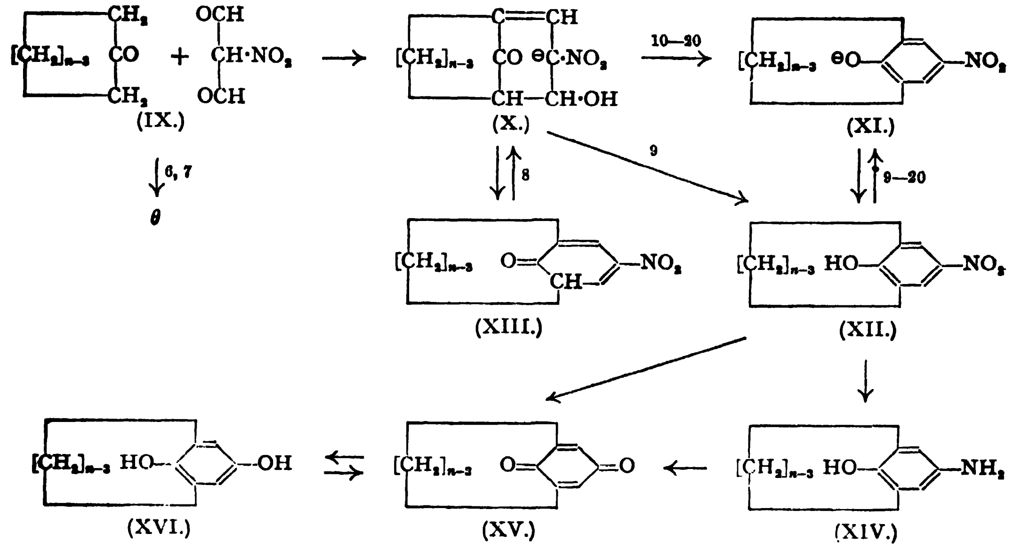


FIG. 12.

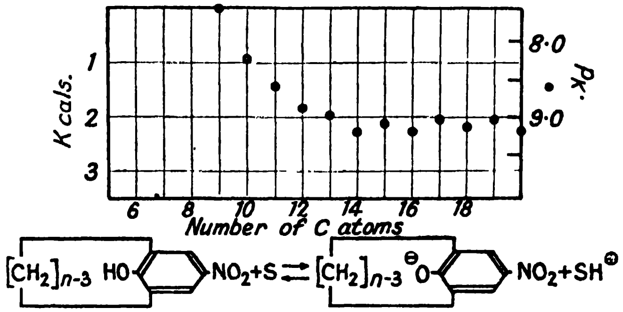
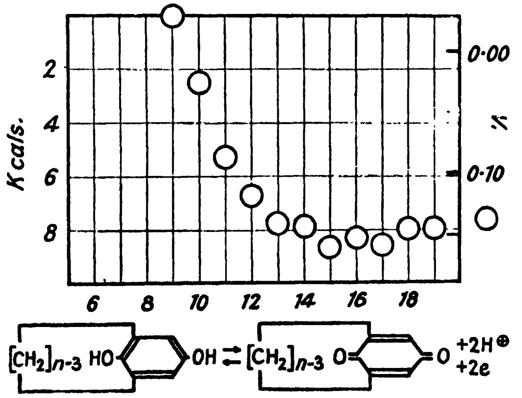


FIG. 13.



We measured the dissociation constants of the *m*-bridged *p*-nitrophenols in 80% Methylcellosolve [31] (cf. Fig. 12) and the redox potential of the *m*-bridged *p*-benzoquinones [33] (cf. Fig. 13).

One can see in both cases that the medium-sized rings stabilise the reaction component with the more nucleophilic oxygen, as would be expected on the assumption of the formation of an intramolecular hydrogen bridge.

I believe that the investigations which we have carried out show clearly that *a medium-size ring effect exists which was not predicted by classical chemistry.* I hope that our interpretation of this effect as a consequence of the constellation and intramolecular interactions of atoms across space is not very far from the truth, and that it can be used as a basis for a more exact theory and as a stimulus for further experiments.

The constellation has hitherto often been neglected as a very important factor which influences the reaction equilibria and reaction rates. The advances in physical approach to this problem will perhaps allow the organic chemist to make in the future more valuable contributions from his standpoint than was possible before.

In conclusion, my best thanks for their wholehearted co-operation are due to my younger colleagues P. Barman, L. Frenkiel, O. Häfliger, H. Günthard, W. Ingold, Margrit Kobelt, K. Wiesner, M. M. Wirth, and M. Zimmermann, who performed the laborious and, in experimental details, not always very interesting work. My thanks are due also to Dr. G. W. Kenner for help in the translation of the manuscript.

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[19] Cf. E. C. S. Jones and J. Kenner, *J.*, 1931, 1849.

[20] V. Prelog and K. Wiesner, *Helv. Chim. Acta*, 1947, **30**, 1465.

[21] V. Prelog, K. Wiesner, W. Ingold, and O. Häfliger, *ibid.*, 1948, **31**, 1325.

[22] V. Prelog and K. Wiesner, *ibid.*, p. 870.

[23] V. Prelog, O. Häfliger, and K. Wiesner, *ibid.*, p. 877.

OBITUARY NOTICES.

ARTHUR PILLANS LAURIE.

1861—1949.

ARTHUR PILLANS LAURIE, the eldest son of the late Professor Simon Somerville Laurie, LL.D., the first Bell Professor of The Theory, History, and Practice of Education in the University of Edinburgh, was born in Edinburgh on November 6th, 1861. He was educated in his native city, first at the Academy, and then at the University (B.Sc., 1881), proceeding later to King's College, Cambridge, of which he was an exhibitioner and prizeman. In 1884, his name appeared in the list of first class Honours of the Natural Sciences Tripos (Chemistry), together with several others, afterwards to become well known in various branches of science. He was elected into a Fellowship of his College in 1888.

About this period, Laurie made the acquaintance of Holman Hunt, whom as time went on he came to know very well. The Pre-Raphaelite master encouraged him to study the scientific aspects of painting, and thus in effect spread out before him the pattern of his life's work. Then, in 1891, Laurie contributed a paper to the Society of Arts Journal entitled " On the Durability of Pictures Painted with Oils and Resins," which won him the Society's Silver medal; in the same year he delivered the Cantor Lectures before the same Society under the title " The Pigments and Vehicles of the Old Masters." Further contributions to the Society's Journal on cognate subjects appeared in 1892, 1893, 1907, and 1922. To read these in retrospect to-day is to realise that they represent the work of a mind of somewhat unusual character, at once versatile and original. Pathfinder and seer, Laurie has not laboured in vain.

Wide interests continued to dominate his busy life. In 1895, he became Lecturer in physics and chemistry at St. Mary's Hospital Medical School, and later was appointed an Examiner for the Royal College of Physicians, and for the City and Guilds Institute. The Home Office Committee on Pottery Manufacture also claimed him as a member. Always interested in educational matters, he was Assistant Commissioner to the Royal Commission on Secondary Education in 1895, and in 1900 accepted the Principalship of the Heriot-Watt College in his native capital. Twelve years later, he added to his responsibilities the Professorship of Chemistry in the Royal Academy of Arts. The first of these appointments he held for 28 years, and the second for 24 years. Meanwhile, in 1895, he had obtained the degree of D.Sc. (Edinburgh), for a thesis entitled " The Constitution of Alloys."

The war of 1914—18 found Laurie in constant request, largely on account of his acquaintance with the late Earl Lloyd George who appreciated the value of his capacity for swift experimentation and breadth of technical experience. He served on numerous Bodies connected with supply and inventions, as well as being concerned with Building Research, to which reference is made later. Running through all these activities can be perceived the influence of a sound " classical chemistry; " his training and outlook supplied the basis for what an earlier generation would have called " experimental philosophy," which Laurie knew instinctively how to apply to the problems at issue.

Between the two wars, Laurie gave much attention to the possibility of using ethyl silicates as stone preservatives; in particular his work on silicon esters should be mentioned. He was a member of the Stone Preservation Committee of the Building Research Board, and then, from 1926—1930, of its Standing Chemical and Weathering Committee. Earlier he had published several papers on stone decay. He conducted experiments at Hampton Court and elsewhere in collaboration with the Ancient Monuments Department of the Ministry (then the Office) of works. In favourable circumstances silicon esters enable the stone to be hardened and consolidated without the introduction of a soluble salt. Later developments have been in other directions, but it is probable that they owe much of their value to Laurie's pioneer interest in ethyl silicates.

Laurie's published work covers an extensive field. His output of books alone is impressive, as the following resume will show—" The Food of Plants " (1893), " Processes, Pigments and Vehicles " (1895), " Greek and Roman Methods of Painting " (1910), " Materials used in the Painter's Craft from the Earliest Times to the End of the XVII Century " (1911), " The Pigments and Mediums of the Old Masters " (1914), " Painters' Methods and Materials " (1926), " Simple Rules for Painting in Oils " (1934), " Pictures and Politics " (1934), " New Light on Old Masters " (1935), and " The Technique of the Old Masters " (1949).

In addition to these volumes, several of them of considerable size and scope, Laurie contributed on various occasions to the usual scientific periodicals. He became interested in the way in which the refractive index of paint media in pictures might serve as an indication of the picture's age. (It is, of course, well known that the medium becomes progressively more transparent with the passage of time; it is this effect which is mainly responsible for the appearance of *pentimenti.*) In 1937 he discussed the sorption of organic liquids by raw linseed oil and stand oil films, and the anomalous results to which it gave rise in the study of the refractive index of such films.

Less known in this country are the articles which Laurie wrote for " Technical Studies in the Field of the Fine Arts " (1933—1942), issued by the Fogg Art Museum, University of Harvard, U.S.A. The following is a complete list, in chronological order:

The Use of an Emulsion as a Painting Medium	1933
Examination of the Masks of Mummified Bulls	1934
Notes on the Medium of Flemish Painters	1934
Materials in Persian Miniatures	1935
Problems connected with the Cleaning and Preservation of Pictures	1935
The Microscopic Examination of the Surface of a Picture	1935
Restrainers and Solvents used in Cleaning Old Varnish from Pictures	1935
The Yellowing of Linseed Oil	1936
The Fayum Portraits Painted in Wax	1937

" Auld Reikie " contributed her garlands as the years went on, the Royal Society of Edinburgh its fellowship in 1885, and the University the honorary degree of LL.D. in 1929. Laurie also became an Honorary Royal Scottish Academician.

He died at Haslemere, Surrey, on October 7th, 1949, and is survived by his only daughter, who shared his life and interests through many years.

He was elected a Fellow of the Chemical Society in 1886.

F. I. G. RAWLINS.

SIR HENRY MIERS.

1858—1942.

FEW Fellows of the Chemical Society can have had a more active, a more varied, and a more useful life than Henry Miers. Save for failing eyesight he never grew old, and for nearly sixty years his alert, tireless, keen, smiling little figure was never idle, ever ready with help and advice, whether it was in the British Museum, Oxford, London, or Manchester. He had many interests, but it was his interest in human beings, his genius for helping others to shape their lives, that so many of us remember with gratitude. Perhaps that is not surprising in the great-grandson of Francis Place, one of the great social reformers of the early nineteenth century, the joint founder of University College, London, and a pioneer in adult education. Miers was proud of his ancestry. His father was a distinguished civil engineer, his grandfather, also an engineer, had travelled widely in South America and in 1843 was elected to the Royal Society for his botanical studies. Miers had an elder brother, Edward John Miers, who was a zoologist on the staff of the British Museum. So science and education were in his blood.

He was born at Rio de Janeiro on 25th May, 1858, and two years later his father retired from his South American business and settled in South London. Miers' preparatory school was Summerfields, just outside Oxford, where that skilful teacher Mrs. Maclaren gave him a taste for classics which lasted all his life. In 1872, like so many of his schoolfellows, he won an Eton scholarship. In his five years at Eton he remained true to classics, eventually winning a classical scholarship at Trinity College, Oxford. However his interests were widening in mathematics and science, and on going up to Oxford in October 1877 he read for both Classical and Mathematical Moderations. He had intended to take both the Honours Schools of Mathematics and Physics, but he was getting interested in crystallography, and hearing that there would soon be a vacancy in the Mineralogical Department of the British Museum he decided to throw up his Science School and devote himself entirely to the competition for that post.

Story Maskelyne was then Professor of Mineralogy in Oxford, but he was also a Member of Parliament living in London; he had no Department and lectured only when required. Miers was his only pupil, but Maskelyne came up each weekend to lecture to him, though the lectures soon degenerated into armchair discussions at the home of the witty Professor of Geometry, Henry Smith, who took a lively part in the talks. What could have been more stimulating for a young and enthusiastic undergraduate?

After taking the Final School of Mathematics, Miers went for three months in 1882 to work in Strasbourg with Groth, with whom he formed a lifelong friendship. The work for his first published paper on cerussite was done during the visit. After all this careful preparation Miers came out top in the Civil Service examination, the only serious competitor being Sanderson, the future headmaster of Oundle.

In October 1882 Miers entered on his new duties at a fortunate moment. The mineral collection had just been moved from Bloomsbury to its fine new quarters in South Kensington, and the new Head of the Department, Lazarus Fletcher, was a kindred spirit who appreciated the fine qualities of his new assistant. Miers helped in the rearrangement of the collection, but he had ample time for research and he took full advantage of the material available for investigation. He remained at the Museum till 1895, and during those years he contributed a long series of papers on the morphology of various crystal species. By them he proved himself an accurate, painstaking investigator, with a quick eye for any abnormality of habit and for points of special crystallographic interest. His most important work was with G. T. Prior on the red-silver minerals, in which they cleared up the relationship of pyrargyrite, xanthoconite, and rittingerite and discovered a new species which was named sanguinite. Although his problems were mainly crystallographic, Miers quickly became a first-class mineralogist. Minerals appealed to his aesthetic taste, he had a wide knowledge of their occurrences and associations, and he was never happier than on mineralogical excursions in Cornwall and elsewhere.

However in spite of the opportunities for research the life of an assistant at the Museum did not for long satisfy the humanism of one who had such a variety of cultural interests. He always longed to be a teacher, and, at the invitation of Arthur Hugh Clough, he gave evening lectures on experimental science, at a neighbouring Board School, to elementary school children. In 1886 his real chance came when H. E. Armstrong, by a stroke of genius, asked him to teach Crystallography in the City & Guilds Technical College. He worked there after Museum hours, and soon built up a small Crystallographic Department which, with the exception of Cambridge, was the first of its kind in this country. Miers' most distinguished pupil was W. J. (afterwards Sir William) Pope, who succeeded him as lecturer in 1895. Pope's first paper was published jointly with Miers, and his early interest in crystals coloured much of his subsequent research.

Miers' energy found many other outlets—foreign travel, visits to most of the great continental mineral collections, and collaboration in a book on " The Soil in Relation to Health," the result of his intimacy with a number of young doctors. His interest in ballooning nearly cost him his life. An aeronaut named Simmons had advertised a balloon flight to Austria, and offered to take one or two passengers. Miers got a few days' leave from the Museum and without telling anyone where he was going he flew off from the Danish Exhibition with Simmons in his large new balloon; the other passenger was a young man named Field. As the wind was from an unsuitable direction Simmons decided to descend for the night near the coast. A strong wind was blowing, and while anchored to a tree near Maldon the whole balloon blew to pieces, and the wire basket with the occupants fell sixty feet to the ground. Simmons was killed, Field broke both legs, Miers was picked up unconscious, and it was six weeks before he could go back to work.

In 1895 came the most spectacular event in his scientific career. He was at the meeting in Burlington House when Ramsay announced the discovery of argon by Lord Rayleigh and himself. The same night Miers wrote to Ramsay suggesting that he should examine the gas given off when cleveite is heated with dilute sulphuric acid, which Hildebrand had thought to be nitrogen. He told Ramsay where he could get the mineral, and six weeks later Ramsay sent the gas from cleveite to Crookes, thinking it might be krypton for which he was looking. Crookes telegraphed back " Crypton is helium. Come and see it." Towards the end of his life an old friend was congratulating Miers on his long innings, saying that in giving the clue to the discovery of helium he hit the ball over the pavilion. Miers replied with characteristic modesty " Oh no ! The helium episode was only a timid but lucky swipe which happened to sneak through to the boundary."

Later in the year Miers was appointed to the Waynflete Professorship of Mineralogy at Oxford in succession to his friend and teacher Story Maskelyne, and in 1896 he was elected a Fellow of the Royal Society. He was delighted to return to Oxford, where he had spent four happy years as an undergraduate, with the prospect of creating a research school of Mineralogy, and with long vacations for foreign travel. The Professorship carried with it a Fellowship of Magdalen, and for thirteen years he gathered round him an ever-widening circle of friends, whom he loved to entertain in his rooms in the New Buildings overlooking the Deer Park.

The rooms in the Museum assigned to the Professor were quickly converted into small but well equipped laboratories for teaching and research, and it was not long before Miers had a small group of keen students. He was an admirable lecturer, and however small the audience Miers gave of his best. Clear and simple, stimulating and full of interest, each lecture was a well-rounded exposition of some topic, which sent us away feeling that for the moment at any rate we understood. I remember as a schoolboy the thrill of hearing his Cantor Lectures on Gem Stones.

Everyone who came under his influence was attracted by his personal interest in them and the happy gift he had of suggesting some subject for research that was within their competence. Among his students were Herbert Smith, who went to the British Museum, H. L. Bowman, who succeeded him in his Chair, T. V. Barker, whose untimely death was a great loss to crystallography, Jacques Chevalier, later Professor of Philosophy at Grenoble, Noel Ashcroft, afterwards President of the Mineralogical Society, and his two assistants R. C. Spiller, now Reader in Mineralogy at Oxford, and R. P. D. Graham, now Assistant Professor of Mineralogy at McGill, who writes of him :

" He was a man of great kindliness, possessed of infinite patience and a disposition that refused to be ruffled. In all the years I was associated with him, I do not recall a single occasion on which he complained, or was impatient, or expressed displeasure when things went wrong or mistakes were made, which doubtless was often enough. Instead, there was always an explanation of the cause of the trouble and instruction as to how it might be avoided in future. These characteristics, and a genuinely personal interest in his students, explain his success as a teacher, for, in his lectures, each individual was made to feel that it was he, personally, who was being addressed. His " Mineralogy," first published in 1902, well illustrates his lucid and systematic method of teaching. It unquestionably set a new standard for textbooks of mineralogy and crystallography. Several that have been published since that time are quite obviously modelled on Miers, and one or two may even be said to mirror it, though in much distorted fashion. But in nearly forty years of teaching experience, the writer has failed to meet with a better ' Introduction to Mineralogy ' than that given us by Miers."

Miers' most important work at Oxford had its origin in his earlier crystallographic papers when his accurate measurements so often showed the existence of differences in interfacial angles even on the same crystal which were much larger than the errors of observation. Previous attempts to elucidate the problem of these " vicinal " faces by elaborate series of measurements on mineral crystals had been unproductive, and Miers decided that the most helpful method of attack was to measure the angles of crystals actually growing in solution. For this purpose an inverted goniometer was built by Troughton & Sims with which the angles of growing crystals could be measured, including the small angles between a group of vicinal faces by means of a new form of micrometer eyepiece. Most of the work was done with cubic crystals (the alums and sodium chlorate) as there was then no doubt as to the theoretical values of the interfacial angles. The experiments showed that crystal growth under these conditions takes place on groups of vicinal faces inclined at small angles ranging from 3′ to 20′ to the cubic or octahedral face under examination. A few crystals belonging to other systems were examined and the same phenomenon was found. During the growth of a crystal sudden changes occurred in the inclination of the vicinal faces. These changes always occurred *per saltum* and not continuously, showing that new plane crystal face had come into existence, and that growth did not give rise to curved faces. There were indications that the inclinations to the normal face increased with increasing concentration, but the experiments were not definite on this point.

The results thus justified Miers' intuition that the study of growing crystals was the best way of advancing our knowledge of vicinal faces, as, without knowledge of the whole history of the growth of a crystal, measurement of its final condition might lead to quite erroneous conclusions.

Miers pointed out that the vicinal faces correspond to a much more open packing of the molecules than the normal faces, and that as the molecules are much more densely packed in the crystal than in the solution (45 times in the case of alum solution) it might be easier for the molecules to be deposited in the more open layers. Miers' paper was a most enlightening contribution to a problem that had puzzled generations of crystallographers, and one wishes that he had pursued it further and by growing crystals under carefully controlled conditions had investigated the factors that cause the variations in the vicinal faces. His attempts were, however, diverted to another aspect of crystal growth. He determined the concentration of the solution in contact with the growing face by using the crystal as a prism to measure the refractive index of the solution. This involved the determination of the effects of temperature and concentration on the refractive index of the solution. In the course of the measurements Miers and Miss Florence Isaac, who joined him in the investigation at this stage, found that the refractive index of a cooling solution increased rapidly until a few crystals began to form, and that at a later stage the refractive index fell rapidly as a cloud of crystals was suddenly produced. I found them one day in the laboratory rather puzzled by this, and suggested that these effects might be due to the transition of the supersaturated solution from the metastable to the labile state as predicted by Ostwald. Trials made by cooling aqueous solutions in sealed tubes showed that crystallisation did not occur spontaneously until a considerable degree of supersaturation was reached, the metastable region being represented by the area between the solubility curve and the curve which Miers named the supersolubility curve, showing the concentrations at which spontaneous crystallisations take place.

Together with Miss Isaac, he undertook a number of investigations of the conditions under which spontaneous crystallisation occurred both in aqueous solutions and also in mixtures, as he thought this was of importance in throwing light on the crystallisation of igneous magmas. With Jacques Chevalier too he investigated the differences in the growth of crystals in the metastable and labile regions.

Another outcome of this work was Miers' interest in the effect of one species in affecting the deposition of others which led to the comprehensive study by T. V. Barker of parallel overgrowths resulting in the discovery of a number of interesting relationships.

Miers made full use of the Long Vacation for foreign travel. Visits to the United States and Canada, and then to Russia to learn the language, were followed by an adventurous trip to Klondyke in 1901 at the invitation of the Canadian Government. In 1903 he went to South Africa at the invitation of the Rhodes Trustees to look into educational problems, and again two years later for the British Association meeting at Johannesburg, when he was President of the Geological Section.

Oxford soon discovered in Miers a most valuable recruit for University business. His equanimity, wide interests, and readiness to help, and his untiring energy were a great asset to the University. As Secretary to the Museum Delegates he took a very active part in the administration of the Museum. Most of the stone capitals had been carved by the brothers O'Shea under Ruskin's supervision, but some were still unfinished. Miers found a benefactor with whose help the remainder were carved with floral designs following the original tradition. He served as a delegate of the University Press, a member of the Hebdomadal Council, and as Junior Dean and Vice-President of Magdalen, while at the same time he had many duties in London as Editor of the *Mineralogical Magazine*, President of the Mineralogical Society, and Vice-President of the Chemical and Geological Societies.

It was Miers' constant touch with the outside world that made him a particularly valuable member of the University. But as a result his reputation as an administrator got abroad, and in 1908 he was invited to succeed Sir Arthur Rücker as Vice-Chancellor of London University. Miers felt it was his duty to go although he hated giving up his teaching and research. He had often said that he wished to make way for younger men and was afraid of the stagnation of advancing years in Oxford.

He went to London at a difficult moment. The University was divided and unsettled by the strong antagonisms between the external and internal parties, which were intensified by the fact that Lord Haldane's Royal Commission on the University was sitting and taking evidence. Miers' time was largely taken up by meetings of Councils and Committees. He was a member of the Governing Bodies of all the constituent Colleges, and there were innumerable problems to be faced. Miers had very happy relations with Lord Rosebery, the Chancellor of the University, and his unbiassed Chairmanship of the Senate was a great help at a difficult period. In 1912, the year he was knighted, Miers, against considerable opposition, persuaded the Universities of Great Britain to hold a Congress of the Universities of the Empire in London. This led to the foundation of the Universities Bureau and to future quinquennial meetings of the Congress.

In London Miers missed more and more the close personal relations with students, and when the war came he saw that the recommendations of the Haldane Commission might not be implemented for many years. So in 1915 he accepted an invitation to go to Manchester as Vice-Chancellor, as he felt he might be more useful in a smaller University, particularly as he was also to be Professor of Crystallography and to do some active teaching.

It was a successful experiment, and Miers spent eleven very happy years in Manchester. His modesty, his friendliness, his range of interests, and his charm as a guest or host quickly won the hearts of the Lancastrians. He threw himself into their problems, not only at the University but in the intellectual life of the community, and he did a great work in bringing the City and the University much closer together. He became the social focus of the University, and he gave both to its graduate and undergraduate life a more closely knit personal structure, which is much more difficult to achieve in " Red Brick " than in one of the older residential universities.

It was not an easy time for a Vice-Chancellor. First he had the war problems, and then the period of reconstruction. But under Miers' care the University gathered strength, and his Vice-Chancellorship was marked by many new developments. Under his sympathetic guidance the University took its full share in civic activities.

He was particularly happy once again to be Professor of Crystallography. He lectured regularly with his old skill, and whenever he could snatch an hour from official duties he was in the laboratory helping the students with that encouragement and personal interest that so many of them remember with affection. He was too busy to do any research himself, but he took the keenest interest in the work that was in progress, very happy that it was in his own field, the effect of environment on crystal growth.

His term of office would normally have ended in 1923, but the Senate pressed him to remain until 1926. When he left he must have been touched by the warmth and spontaneity of the many tributes from the University and the City for all that he had done for them.

In 1926 he returned to London and bought a house in Hampstead, meaning to return to his scientific work. But it was not to be. First there were jobs to be rounded off, and then, ever willing and eager to help in any constructive work, he was drawn into fresh activities.

In 1926 he undertook a Report on our Museums and Art Galleries for the Carnegie United Kingdom Trustees with S. F. Markham as his Secretary. As a result Museums became his chief occupation and interest for the rest of his active life. He served on the Royal Commission on Museums and on the Standing Committee appointed to carry on its work. He was President of the Museums Association for six years and with Markham he made a survey of the Museums in the Empire for the Carnegie Corporation. Miers was convinced of the great part Museums could be made to play in the life of the people if they were recast and for ten years he was the acknowledged centre of progress in all museum work.

As the years wore on, even his tireless energy began to flag, and when his eyesight failed and made travelling difficult the Museum work was left more and more to Markham. But he was never idle, and in these last years his happiness was the collection of plants in the London district and the care of his collection of photographs of classical sculpture. He never lost his enthusiasms and his interest in the doings of friends and pupils.

Miers's life was spent in the service of others. He was a fine teacher of the most generous type, clear and encouraging, and making everyone feel that there was a place for him in the world. Modest, unselfish, loving his fellow men, he was perhaps a little too gentle at moments in debate when a firm lead was needed. But he was a great humanist, and at times like these when the ethical influence of science is often called in question, Miers is an example of what a man of science can do in applying scientific methods in administration, and to the wider problems of academic and national life.

HAROLD HARTLEY.

SIR ROBERT ROBERTSON.

1869—1949.

THE death of Sir Robert Robertson at the age of eighty removes from our midst a man of outstanding personality. Primarily an expert of world-wide repute in the field of explosives, he had a great variety of other interests, mainly scientific, but including also such subjects as classics and historical research. He was a Fellow of the Chemical Society for over forty years and was twice a Vice-President.

Robert Robertson was born on April 17th, 1869, in Cupar Fife, and was the son of J. A. Robertson, D.D.S. Both the father and the grandfather had somewhat of a scientific bent. Robert was the eldest of a family of four; of his three sisters one, Jess Isabel, married William Rintoul, a colleague of Robertson's in his explosive work. Robertson was married in 1903 to Kathleen Stannus, daughter of Hugh Stannus, F.R.I.B.A., lecturer in Applied Art at South Kensington and Manchester. She inherited his artistic ability and has produced many charming works of art. She died in 1938. Two children, a daughter and a son, survive Sir Robert.

1876—1885.

At the age of seven Robertson entered the Madras Academy, Cupar Fife. The curriculum did not include science, but a small laboratory was fitted up at home. He showed great industry at school and gained many prizes. On leaving, he was awarded the Balgonie Gold Medal. In the Senior Local Examination of St. Andrews University he was placed first in Scotland and won the University prize.

1885—1890.

Robertson matriculated at St. Andrews University in October 1885 for the M.A. degree. In the 1885—1886 Session there were sixty "bejant" students, as they are called at St. Andrews in their first academic year. Two of these, Robert Robertson and Alexander MacKenzie, attained the distinction of the Fellowship of the Royal Society.

The course extended over four Sessions. No chemistry classes were included; it was, however, possible to take extra classes if time permitted and Robertson found that he could attend classes in science in his third and fourth years, which would enable him to qualify for the B.Sc. degree. A fellow student, David Lawson, who had attended Purdie's chemistry lectures, spoke enthusiastically to Robertson about them and he decided to enter for a chemistry class. In the following year he took a more advanced class and came for the first time under the stimulating influence of Purdie. This made a tremendous impression on him and ultimately a life-long friendship sprang up. Robertson took the M.A. degree in 1889, and in 1890, after a further summer course, he took his B.Sc. degree.

His affection for his old University was almost a passion. In his later life he was a founder member of the St. Andrews Club, London (1904), and was for many years Chairman of Council. He was always interested in historical studies and made a study of the Avignon Popes of whom the last, Peter de Luna (Benedict XIII), founded St. Andrews University in 1411.

1890—1892.

On leaving College, Robertson entered the laboratory of the City Analyst in Glasgow and worked under Robert T. Thomson (who recently completed his fiftieth year as a Fellow of the Chemical Society). Through him, Robertson made the acquaintance of James Miln Thomson, manager of the Cordite Section of the Royal Gunpowder Factory at Waltham Abbey, and this was destined to lead his steps into the explosives world.

1892—1907.

In 1892 Robertson was appointed as a junior chemist (at twenty-seven shillings a week) under J. M. Thomson. Thomson encouraged his young assistants to undertake investigations, to give them a greater interest in their work. He set Robertson to work on the relationship between the nitrogen content of nitrocellulose and its solubility in ether–alcohol. Robertson also made experiments on the preparation and properties of ethylene dinitrate, and on the basis of this work he obtained the D.Sc. degree of St. Andrews University in 1897.

A further practice, instituted by J. M. Thomson, was that his young chemists should spend six months learning factory operations side by side with the workmen; thus Robertson acquired a first-hand knowledge of the processes.

In 1894 there was a serious explosion in the nitroglycerine plant. With great pluck Robertson and two others "drowned" the remaining nitroglycerine in water and thus probably averted a further explosion. For this act he was presented with a gold watch by the Government. He regarded this watch as one of his most valued possessions. He was placed in charge of the nitroglycerine manufacture until 1900. During this time he and William Rintoul worked out a process for recovering acetone vapour, which had previously been allowed to go to waste in the cordite driers. This depended on absorption by sodium hydrogen sulphite and was applied on a very large scale.

In 1900 Robertson was put in charge of the Main Laboratory. He had a certain amount of time available for research and made a study of the Will stability test for nitrocellulose in its application to the purification of gun-cotton by boiling with water. He found that the best method of purification was to boil the gun-cotton initially with weak acid to hydrolyse unstable impurities; the acids could then be removed by prolonged boiling with water. This valuable discovery was published in 1906 and has become the standard practice in gun-cotton manufacture. He followed up this work by modifying the Will test to adapt it to the measurement of the rate of decomposition of nitroglycerine.

In a further research with S. S. Napper the absorption spectrum of nitrogen dioxide was examined and it was found that nitrogen dioxide could be detected and measured in low concentrations in air. This was utilised to measure the gradual decomposition of nitrocellulose at medium temperatures.

At about this time some of the cordite came under suspicion of having inflamed spontaneously. The Will test threw no light on this, and Robertson introduced a new stability test, the "Silvered Vessel Test." The cordite was ground and heated at 80° in a vacuum-jacketed and silvered flask. The decomposition was detected, first by visible fumes of nitrogen dioxide and then by a rise of temperature. The cordite then in use contained 5% of mineral jelly, and he found that if the mineral jelly were omitted or replaced by saturated hydrocarbons the stability was greatly decreased. From this it was deduced that mineral jelly contained a small proportion of hydrocarbons which reacted with nitrogen dioxide. Since nitrogen dioxide acts as an auto-catalyst in the decomposition its removal is beneficial to the stability.

A field of work which was the subject of considerable investigation by Robertson was the calorimetry of the explosion of cordite. This was based on the work of Sir Andrew Noble. The cordite was placed in a thick-walled steel bomb which was immersed in a calorimeter. The effect of mineral jelly and of the proportion of nitroglycerine was measured.

1906—1907.

In the summer of 1906 spontaneous explosions took place in two magazines in India. This required urgent investigation, and Colonel Nathan and Dr. Robertson were sent out to India to undertake this. The Silvered Vessel Test proved its value in correlating the decline of stability with the temperature and time of storage, and it was possible to lay down a safety limit, below which the test should not be allowed to fall. An exhaustive report was made on the conditions of storage with recommendations for the preservation of cordite in hot climates, and this remained for many years a classic source of reference.

1907—1914.

On his return from India early in 1907, Robertson was invited to take up the position of Superintending Chemist at the Woolwich Research Department. This Department had been in existence for about six years. It arose out of an experimental establishment set up by the Explosives Committee. The Committee included a number of illustrious scientists, among whom were Lord Rayleigh, Sir William Crookes, and Sir Andrew Noble. They took a personal interest in the work, which was very encouraging to the small staff of about half-a-dozen chemists. The original terms of reference were to improve the detonation of lyddite and to overcome the defects of the cordite at that time in use. The work, however, widened rapidly; many explosives were synthesised and examined, notably trinitrophenylmethylnitramine, for which a manufacturing process was worked out. Important work on the stability of propellants was carried out and the study of trinitrotoluene was commenced. New and well-equipped laboratories were built and the work expanded greatly. Unfortunately, the scientific Explosives Committee gave place in 1906 to a Board in which science had relatively little representation and in 1907 a military "Superintendent of Research" was appointed. Such was the background of the Department at the time of Robertson's appointment on April 7th, 1907. His University course for the M.A. degree had left him relatively little time to obtain a comprehensive knowledge of chemistry, but he brought a valuable fund of technical experience and a useful knowledge of safety precautions to the Department. His organising ability had full scope; he was a good administrator and had abundant energy; painstaking, methodical, and cautious in arriving at decisions, but obstinate in adhering to them in the face of any opposition. He was domineering and issued his instructions in the form of abrupt and peremptory orders. The junior members of the staff were terrified of him.

He realised the necessity of amassing a systematic fund of information on all subjects connected with explosives. This aided in dealing with the increasing influx of Service problems.

In view of its importance the stability of cordite was one of the most prominent subjects of investigation. The deterioration of cordite starts from minute nuclei of impurities and spreads by autocatalysis. An exhaustive study of the nature of the harmful impurities was made by means of climatic storage trials. This led to a better control of the cordite stored in magazines and to the introduction of precautions in the manufacture.

Work on high explosives was also in progress. A comprehensive study of the properties of trinitrotoluene was made and the manufacture and purification of trinitrophenylmethylnitramine were perfected. Important researches on the initiation of detonation of high explosives and the sensitiveness of explosives to impact were carried out. Robertson showed a keen interest in the progress of the work; he also fulfilled a useful function in establishing contacts with other Service departments. The opportunities for publication were very restricted on account of its secrecy.

1914—1918.

With the outbreak of war in August 1914 the Research Department was put to a strenuous test. With a staff of nine chemists and subordinate staff it was required to cope with a host of problems in a minimum of time. The work was so wide-spread that it cannot be dealt with in any detail. A few outstanding examples may, however, be mentioned.

In October 1914 improvement in the supply of trinitrotoluene (T.N.T.) became extremely urgent. Robertson was asked whether his Department could make three tons a week of T.N.T. to relieve the position. He immediately gave orders that work should be put in hand at the highest pressure to establish the most efficient method of manufacture. The existing processes were slow and inefficient. They also required oleum, which was not available. Intensive laboratory work was put in hand and a number of radical improvements were worked out. After a short time the work had reached a stage at which an experimental plant could be designed. Robertson's technical knowledge then stood him in good stead; he made a personal search of the scrap heaps of Woolwich Arsenal to find the necessary equipment and a plant for three tons a week was soon erected. This gave successful results and it was kept in production for a considerable time. In the early stages the supply position was so crucial that each week's output was seized upon with avidity for shell-filling, etc. This process was taken as the basis of the design of the large-scale Government plant at Oldbury and later that at Queensferry.

Although this work led to the expansion of T.N.T. production to a very large scale, it was still limited by the available toluene and it soon became evident that a still larger supply of high explosive would be required. In order to eke out the T.N.T. the use of a mixture of T.N.T. and ammonium nitrate was investigated at the Research Department. Trinitrotoluene is in itself deficient in oxygen whilst ammonium nitrate has a slight excess. A balanced mixture would be obtained by adding about four parts of ammonium nitrate to one part of T.N.T. At that time it was necessary to add about 40% of T.N.T. to enable the mixture to be melted to a slurry and poured into shells, but this was remedied later and made it possible to use the mixture containing 80% of nitrate. The detonation of this mixture was a difficult matter and numerous other difficulties arose such as hygroscopicity, corrosion of metals owing to hydrolytic dissociation, formation of dangerous salts with copper, etc., decomposition of T.N.T. by traces of pyridine and thiocyanate, transitions of crystalline form at −16°, 32°, 85°, and 125°. The ammonium nitrate had to be made from Chile saltpetre by double decomposition and was difficult to purify. These difficulties were overcome step by step and this " dilution " of the T.N.T. enabled the quantity of available high explosive to be increased enormously. The mixed explosive was named " Amatol." (I have refrained from mentioning names of the staff working under Robertson, but think that the name of E. R. Deacon, who has since passed away, should be put on record for his valuable work on amatol.)

Another difficulty was that amatol gave little or no smoke on detonation and this made it difficult to locate the burst of the shell. To remedy this, smoke mixtures were devised and incorporated into the shell filling.

Meanwhile serious difficulties arose in the production of cordite owing to shortage of acetone. It was necessary to devise a propellant of the same ballistic properties as cordite M.D. without using acetone; it was also necessary that manufacture should be capable of being carried out in the existing plant. This was met by the introduction of a new propellant, " Cordite R.D.B.", in which the solvent used was a mixture of ether and alcohol. This propellant was ultimately manufactured in enormous quantities in the largest propellant factory at Gretna.

As the war proceeded, the difficulty of obtaining chemists for research work and for manning the factories became more and more acute. Scientists had been sent to the Front regardless of their value in producing vital supplies of munitions. It is amusing to read in a leaflet issued by the Parliamentary Recruiting Committee the advice given for Enlistment in Special Corps : " Men specially enlisted (a) such as Navvies, Tunnellers and Chemists."

In 1917 Robertson went to France and interviewed many scientists. This ultimately led to the return of valuable scientific workers to this country.

At the end of the war in 1918 the staff of scientists numbered one hundred and ten. When the news of the Armistice arrived, Robertson and a group of the staff were engaged in a conclave. It was typical of Robertson that he solemnly proceeded with the discussion and for another hour the scientists had to possess themselves in patience and continue the discussion.

During the war Robertson worked untiringly. He made a point of visiting the laboratories as often as possible to get first-hand information on the progress of the work. I think it may be said that this formed the peak of his long and active career. He was in the prime of life and rendered truly great services.

It was during the first World War that he was elected a Fellow of the Royal Society (1917). In 1918 he was created a K.B.E. in recognition of his valuable work.

1919—1921.

Much research work remained to be done after the war, but the staff dwindled rapidly after the Armistice. Robertson's time was very much occupied in the question of reorganisation of the conditions of employment of scientists. He continued to be a member of the Ordnance Committee and several other Committees until he left the Department on March 6th, 1921.

1921—1936.

On the retirement of Sir James Dobbie, F.R.S., from the post of Government Chemist, Sir Robert was appointed to this position and took up his duties on March 7th, 1921. In the Government Laboratory, which was already very efficiently organised, he was free to devote himself to work which was congenial to him. He took part in many committees and found time for private research.

The post of Government Chemist carries with it other duties, as he is Chief Agricultural Analyst, Referee under the Food and Drugs Act, and Advisor to the Board of Customs and Excise. The magnitude of the work of the Government Laboratory can be judged to some extent from the impressive Annual Reports. It increased largely during Sir Robert's tenure, owing to legislation such as the Safeguarding of Industries Act, etc.

Apart from the routine analytical work, special investigations were carried out at the Laboratory to assist Departments of State, *e.g.*, the carriage of dangerous goods at sea, the elimination of sulphur dioxide and nitrous gases in the atmosphere, the effect of lead tetraethyl in petrol on health, the investigation of the mineral resources of the Dead Sea for the recovery of potassium chloride, bromine, etc. Sir Robert served on numerous Committees dealing with these and other subjects.

Research on Infra-red Absorption Spectra.—Robertson's great wish was to devote himself to research. He told me that he felt he must do research " to save his soul." The work on infra-red spectra dealt with the three hydrides NH_3, PH_3, AsH_3. Robertson's interest in the subject arose out of the explosive nature of arsine gas, and the original object was to determine whether its decomposition would be accelerated by exciting the molecule with one of its vibrational frequencies. He was fortunate in having the collaboration of J. J. Fox. who had considerable experience in spectroscopy. The work was described in a series of papers in the *Proceedings of the Royal Society* by Robertson, Fox, and Hiscocks.

Special precautions were necessary to overcome the effects of electro-magnetic disturbances and mechanical vibrations caused by heavy road traffic. A tetrahedral structure was deduced for each of the three molecules, though not of equal height. The moments of inertia were calculated. In addition to the rotation system shown by PH_3 and AsH_3, NH_3 was found to have a further system of rotation. Beer's law was found to hold accurately. At that time there were very few infra-red spectrometers in the whole world. There is no doubt that the work of Robertson and his colleagues greatly stimulated infra-red spectrometric work in this country and abroad.

Research on Diamonds.—The published work on the infra-red spectrum of diamonds showed some discrepancies and Robertson proceeded to make a study of diamonds from different sources. In the examination of the first six diamonds one behaved abnormally. The other five gave a strong absorption band at 8 μ. but the sixth gave no such band. Later, other examples of this abnormality were found. Differences were also found in the ultra-violet. Other physical properties were examined; some of these properties showed differences between the normal diamonds (Type I) and the abnormal (Type II). In all, six abnormal diamonds were found, out of a total of three hundred examined. The joint work (Robertson and Martin) was summarised in the Jubilee Lecture to the Society of Chemical Industry (*Chem. and Ind.*, 1944, 18) in which the significance of the physical properties was discussed and surmises were made as to the conditions of formation of the two types in Nature.

Robertson took some interest in the question of the artificial production of diamonds and examined the minute specimens left by J. B. Hannay to the British Museum in 1880. At least one of these proved to be of the abnormal type.

1936—1939.

Robertson retired from the Government Laboratory on April 16th, 1936. He continued, however, to serve on several Committees. In 1937 he resumed experimental work at the Davy Faraday Laboratory. He designed and made apparatus for the exploration of spectra into the deep infra-red, *i.e.*, from 100 μ. downwards. In the middle of 1939 the war clouds became ominous and at the age of 70 he offered his services to his old Research Department at Woolwich.

1939—1945.

At the outbreak of the war, the work of the Research Department was decentralised. Robertson was placed in charge of the section which was stationed at University College, Swansea. The work was already well organised and Sir Robert was thus free to spend a large proportion of his time on Committee work under the Scientific Advisory Council, where his wide knowledge of explosives was of great assistance. In 1939 he was appointed Chairman of the Committee on Higher Explosives. From 1940 to 1942 he was Chairman of the S.A.C. Committee on Chemistry of Explosives and Physics of Explosives. He served also on a number of other Committees. The attendance at the meetings in London involved a great deal of travelling and included some hundred night journeys, an effort which would have taxed the strength of many a younger man. He was awarded the Davy Medal of the Royal Society in 1944 in recognition of his valuable services to Science and the Nation.

1945—1949.

At the end of the war Robertson had attained the age of 76, but was still full of vigour. He resumed his work at the Davy Faraday Laboratory, perfecting the technique of infra-red work and experimenting on the synthesis of diamonds. He extended Hannay's work and endeavoured to obtain crystalline carbon from solutions of cyanides in molten silver and other metals.

He was a member of the Armaments Research Advisory Board until his death. He was Chairman of the Committee which dealt with the Armstrong Memorial Fund (1945—1948). He continued as a Censor of the Royal Institute of Chemistry until 1946.

In 1947 he took an active part in the Centenary Celebrations of the Chemical Society. He was Chairman of an Exhibition at the Science Museum illustrating the achievements of British chemists during the last one hundred years and brought together a remarkable collection of apparatus of historical interest.

In 1948 he was appointed Editor in Chief of a comprehensive work on "The Science of Explosives," but after putting much work into this he was ultimately compelled by failing health to relinquish the Editorship.

He was practically free from illness until the early part of 1948, when he had a bad heart and congestion of the lungs. His tough constitution pulled him through, but he was much weakened. In 1949 he had influenza and broncho-pneumonia and passed away at his home in London on April 28th, just eleven days after his 80th birthday. He might almost be said to have died in harness, and I am sure he would not have wished it otherwise.

Thus ended a long and strenuous career. It was probably fortunate for him that he had to forge his way by hard work in his early years. From the beginning he strove after success and achieved it in a high degree. His honours included a presentation gold watch from the Secretary of State for War in recognition of gallant behaviour after a serious explosion in 1894, the Fellowship of the Royal Society in 1917, the K.B.E. in 1918, LL.D. St. Andrews in 1923, the Silver Jubilee Medal in 1935, the Coronation Medal in 1937 and the Davy Medal of the Royal Society in 1944.

In all that he undertook he worked tirelessly and conscientiously; his tenacity of purpose carried him through many difficulties. He was supremely self-confident, frequently autocratic and domineering. His tough constitution enabled him to retain his vigour into old age and his studious disposition remained with him to the end. He strove after recognition, but he had also his sentimental side; he was greatly attached to his old University and to his chemistry professor, and had many other intimate friends for whom he had a real affection.

International Relationships in Chemistry.—An account of Robertson's activities would be incomplete without some reference to his efforts to further co-operation and friendly intercourse with scientists abroad. As President of the Chemical Section of the British Association at Toronto in 1924 he made many lasting friendships. Whilst on the American continent he travelled to Vancouver and back, and then to the United States, where he established profitable relations with our fellow-scientists. In 1927 he visited Paris as Royal Society representative at the Berthelot Celebrations and made a further visit in 1931. In 1930, and again in 1934, he visited Belgium and Northern France in connection with the problem of water-pollution. In 1934 he attended the International Congress of Chemistry at Madrid and in 1936 he visited Roumania, Istanbul, and Austria. In 1937 he went again to Paris for the Congress of Industrial Chemistry, and in 1938 he took part in the International Congress of Chemistry at Rome. He readily got on to a friendly footing with scientists abroad and in return he welcomed them on their visits to this country and showed them hospitality at his home. In so doing he rendered a real service to Science. With him national boundaries formed no barrier to the establishment of fraternal relations. During the war of 1939—1945 he was in very frequent contact with the Canadian and American representatives and did much to promote their co-operation.

In this connection the " Catalysts' Club " should be mentioned. It was established about thirty years ago, and one of its purposes was to entertain distinguished foreign visitors to this country having similar interests to those of the Club. Robertson took an active part in this and often presided at the meetings. The Club was well named and Robertson was distinctly a good catalyst. He was good company and, as one member put it, they liked his pawky humour.

Societies and Institutions.—Robertson's loyal devotion to the learned Societies was a feature which greatly impressed his colleagues and friends and he attended, and often presided at, a great number of scientific meetings.

Royal Society. Robertson was elected a Fellow in 1917. He served on a number of Committees, including the Committee on Applied Sciences (1919—1922) and the Committee for exhibit on Pure Sciences at the British Empire Exhibition (1922). He represented the Royal Society on the General Board and Executive Council of the N.P.L. (1925) and in the Berthelot Celebrations at Paris (1927). He was awarded the Davy Medal in 1944.

Chemical Society. He was elected as a Fellow in 1907 and was a Member of Council 1919—1922. He was a Vice-President in 1926—1929 and again in 1936—1939. In 1922 he represented the Chemical Society on the Conjoint Board of Scientific Societies. His activities in connection with the Centenary Celebrations are mentioned above.

Faraday Society. Elected 1920, he became a Member of Council in 1921 and was President in 1922—1924.

Royal Institution. Robertson was a devoted member of this Institution. He was elected in 1921, became Manager in 1924, Secretary 1926—1929 and Treasurer 1929—1946. During this time he acted as Vice-Chairman. When the renovation of the theatre and various building became urgent he took an active part in obtaining the necessary funds (about £100,000). During the Faraday Centenary Celebrations in 1931 he frequently presided at meetings.

British Association. Robertson was President of Section B (Chemistry) at the Toronto meeting of 1924.

Royal Institute of Chemistry. He became a Fellow in 1897, Member of Council 1915—1918 and 1921—1932, Vice-President 1918—1921.

Salters' Institute. Robertson was appointed Director in 1937 and continued to hold this post until shortly before his death.

London University. Member of Board of Studies for Chemistry and Chemical Industry 1921—1925 and 1944. Board of Advisors in Chemistry.

Ramsay Fellowships. Member of Advisory Committee 1921.

Ramsay Chemical Engineering Department. Member of Committee.

He was also a member of a number of other Scientific Societies and of the Royal Society Club and the Athenæum. His activities in connection with the St. Andrews University Club, London, have already been mentioned.

He maintained a close connection with the Scottish Universities through his position as Advisor in Physical Chemistry under the Carnegie Trust. R. C. FARMER.

F. E. WHITMORE.

1923—1949.

FRANK EDWARD WHITMORE lost his life on July 25th, 1949, at the age of 26 in a climbing accident in Switzerland and his death came as a severe shock to his former teachers and to his colleagues and many friends in Birmingham.

Whitmore, one of three talented brothers, received his early education at Handsworth Grammar School from which he entered the Chemistry school of the University of Birmingham in 1942. Always a brilliant scholar, he duly graduated with first class Honours and was awarded a Teaching Scholarship in the Chemistry Department.

He engaged in research work under Dr. F. J. Llewellyn in the *X*-ray department, studying the single-crystal *X*-ray methods of determining the crystal structure of organic substances (explosives). With Llewellyn he published some of the work in the Journal (*J.*, 1947, 881).

On gaining his Ph.D. in 1946 he was appointed to an I.C.I. Fellowship which he held in the Department of Physics at Birmingham with the object of building up, with the unusual facilities available, a small group engaged in studying radiochemistry. In addition it was the object of his new group to look after general chemical problems of the Nuclear Physics laboratory and to provide a link with interested workers in the Chemistry Department. From the start, owing to his generous and helpful nature, this new venture was a marked success and in his researches Whitmore had already begun to make a name for himself. He was particularly interested in the chemical state of atoms newly formed by nuclear transformation, *e.g.*, in the cyclotron. He paid a good deal of attention to phosphorus 32, and showed that this element when made by the action of fast neutrons on the sulphur in sodium sulphide appears, when brought into aqueous solution, as a phosphate ion. Several papers on this work were in preparation for the press when he was killed.

His particular hobby was mountaineering and he was an enthusiastic, generous and able leader among Midland climbers. He had an unusual talent for amateur dramatics and in his undergraduate days was in great demand by the various University societies, particularly the University Chemical Society.

He was unmarried and leaves a widowed mother. Because of the long period of training necessary for such work, Whitmore's untimely end is a sad loss to radiochemistry and to Birmingham, and his place cannot easily be filled.

M. STACEY.

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M. STACEY.

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88. *The Ultra-violet Absorption Spectra of 2 : 2′-, 2 : 4′-, 4 : 4′-Dihydroxydiphenylmethanes, 2 : 2′-Dihydroxy-5 : 5′-dimethyldiphenylmethane and its 3-, 4-, and 5-Ring Polymers, and of 4 : 4′-Dihydroxydiphenylethane.*

By R. F. HUNTER, R. A. MORTON, and (in part) A. T. CARPENTER.

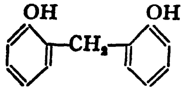
There is a small shift in maximum of ultra-violet light absorption towards the region of longer wave-length on passing from 2 : 2′- to 2 : 4′- and 4 : 4′-dihydroxydiphenylmethane, in agreement with similar difference for *o*- and *p*-substitution observed in the cresols and xylenols. The $-CH_2-$ link gives more satisfactory "insulation" between phenolic chromophores in 4 : 4′- than in 2 : 2′-dihydroxydiphenylmethane, and the insertion of a second $-CH_2-$ link, as in 4 : 4′-dihydroxydiphenylethane, further assists this. The appearance of a second band at 227 mμ. indicates, however, that even here "insulation" is not perfect. Substitution of methyl groups in the *p*-position to the hydroxyl groups in 2 : 2′-dihydroxydiphenylmethane slightly displaces the maximum to longer wave-length, and addition of a further cresol nucleus causes a smaller displacement on passing from the 2- to the 3-ring polymer of 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane; addition of further cresol nuclei, in the 4- and 5-ring polymers, has however no such effect. There is a steady increment of $\varepsilon_{max.}$ of approx. 3000 for each additional aromatic ring. A solution of the "clathrate" complex of the 4-ring polymer and ethylene dichloride gives the same absorption curve as the 4-ring polymer, indicating that the origin of the complex cannot be attributed to any form of enhanced dipole association.

WITH the exception of the paper of de Boer, Houwink, and Custers (*Rec. Trav. chim.*, 1933, **52**, 710) and the later investigation of Mayer-Pitsch and Troger (*Z. Electrochem.*, 1941, **47**, 60) little work has been published on the ultra-violet absorption spectra of resins of the phenol-formaldehyde type or their intermediate products. During an examination of the ultra-violet absorption of certain Novolak and oil-modified Novolak resins, attention was directed to the isomeric 2 : 2′- (I), 2 : 4′- (II), and 4 : 4′-dihydroxydiphenylmethanes and to 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane (III; $n = 0$) and the higher polymers of the last.

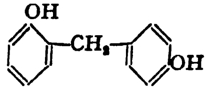
Preliminary measurements by the photographic method showed certain small and interesting differences which it was considered desirable to confirm with the Beckman spectrophotometer. The results obtained for (I), (II), (III; $n = 0$), and the 3-, 4-, and 5-ring polymers of (III), together with those for *o*- and *p*-cresol, *m*-4- and *m*-2-xylenol, and (IV) are given in the table. The detailed ultra-violet absorption curves for some of these compounds are shown in the figure.

Compound.	$\lambda_{max.}$ (mμ.).	$\varepsilon_{max.}$.	$\lambda_{min.}$ (mμ.).	$\varepsilon_{min.}$.
o-Cresol	274	2,015	240	71·9
m-2-Xylenol	274	1,500	241	90
p-Cresol	280	1,995	244	70
m-4-Xylenol	280·5	2,148	245·7	98·2
2 : 2′-Dihydroxydiphenylmethane	275·5	5,110	242	262·5
2 : 4′-Dihydroxydiphenylmethane	277·5	4,490	248·3	462
4 : 4′-Dihydroxydiphenylmethane	280	3,790	250·8	444
(III; $n = 0$)	284	5,400	247·3	256
(III; $n = 1$)	288·5	8,480	248·3	450
(III; $n = 2$)	288	11,800	249	727
(III; $n = 3$)	288	14,725	249	1,250
4 : 4′-Dihydroxydiphenylethane	279	3,730	246	275
	227	17,625	—	—

It will be seen that there is a small shift of the maximum to the region of longer wave-length on passing from 2 : 2′- to 4 : 4′-dihydroxydiphenylmethane, the 2 : 4′-isomer occupying an intermediate position in agreement with the similar differences for *o*- and *p*-methyl substitution in the cresols and xylenols. However, the substitution of a second methyl group in the xylenols has no effect on the wave-length of the absorption maxima of *o*- and *p*-cresol, although there is a curious and substantial drop in extinction coefficient in *m*-2-xylenol. This may perhaps be explained in terms of steric inhibition of resonance (cf. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890).



(I.)



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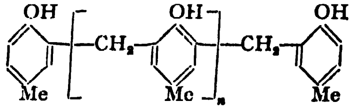
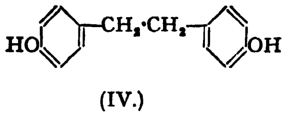
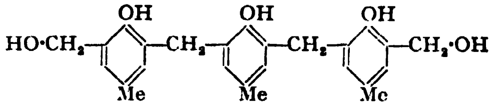


(III.)



(IV.)



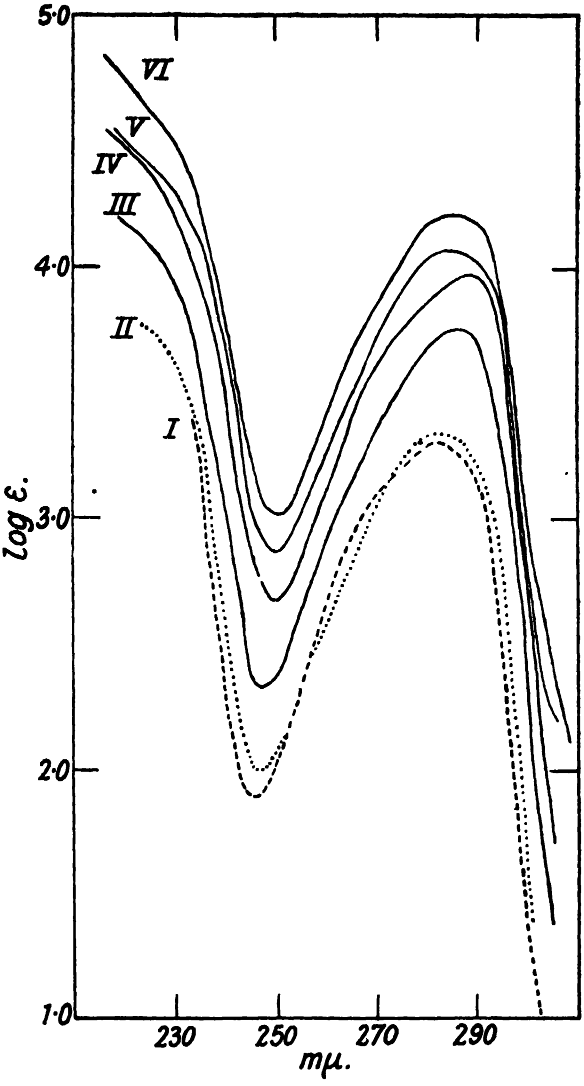
(V.)

The $\varepsilon_{max.}$ and $\varepsilon_{min.}$ values for 2 : 2′-dihydroxydiphenylmethane, which are both greater than twice the respective values for *o*-cresol, show that the $-CH_2-$ link between the phenolic chromophores in the latter does not give perfect " insulation " (cf. Ramart-Lucas, *Bull. Soc. chim.*, 1932, 51, 289). Comparison of $\varepsilon_{max.}$ and $\varepsilon_{min.}$ of 4 : 4′-dihydroxydiphenylmethane with those for *p*-cresol shows that more satisfactory " insulation " occurs in this isomer. The insertion of a second $-CH_2-$ link between the aromatic nuclei in 4 : 4′-dihydroxydiphenylethane (IV) confers still more satisfactory " insulation " of the chromophores (Ramart-Lucas, *loc. cit.*). The appearance of the band at 227 mμ., not shown by *p*-cresol, indicates, however, that even here "insulation " is not perfect (cf. Braude, *J.*, 1949, 1902).

Substitution of methyl in the *p*-position to the hydroxyl groups in 2 : 2′-dihydroxydiphenylmethane causes a slight displacement (7·5 mμ.) of the maximum towards the region of longer wave-length, and the addition of a further *p*-cresol nucleus causes a smaller displacement on passing from 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane (III; $n = 0$) to the tricyclic polymer (III; $n = 1$). The addition of further aromatic nuclei in the tetra- and penta-cyclic polymers (III; $n = 2$ and 3 respectively) is unaccompanied by any further displacement of the absorption maximum which remains at 288 mμ.

There is a steady increment in $\varepsilon_{max.}$ of approximately 3000 for each additional aromatic ring in passing from 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane to the 5-ring polymer, but the $\varepsilon_{max.}$ values for the cresols and *m*-4-xylenol are about 2000, indicating a roughly 50% increase in the probability of the relevant electronic transition. There is also an interesting rise in $\varepsilon_{min.}$ for each successive additional ring, indicating a steadily increasing probability for another transition with growth of the polymer chain.

	$\varepsilon_{max.}$.	Diff.	$\varepsilon_{min.}$.	Diff.
m-4-Xylenol	2,148	3252	98·2	157·8
(III; $n = 0$)	5,400	—	256	
(III; $n = 1$)	8,480	3080	450	194
(III; $n = 2$)	11,800	3320	727	277
(III; $n = 3$)	14,725	2925	1250	523



I. p-*Cresol.* II. m-4-*Xylenol.* III. 2 : 2′-*Dihydroxy*-5 : 5′-*dimethyldiphenylmethane.* IV. 3-*Ring polymer.* V. 4-*Ring polymer.* VI. 5-*Ring polymer.*

If the values for $\varepsilon_{\text{max.}}$ and $\varepsilon_{\text{min.}}$ are plotted against the number of aromatic nuclei, there is a good approach to linearity for the former and a less satisfactory one for the latter.

While the results therefore plainly show that the series is as a first-order problem simply additive, the second-order constitutive effects are by no means negligible.

In the course of attempts to purify the 4-ring polymer (III; $n = 2$) by recrystallisation from ethylene dichloride the formation was observed of an extraordinary stable crystalline 1 : 1-addition complex of this compound with the solvent which survived heating to 90° in a high vacuum (molecular distillation conditions). The ultra-violet absorption spectrum of a solution of the addition complex gave the same curve as the 4-ring polymer when molecular extinction coefficients were calculated on the basis of a 1 : 1 mol. ratio of the latter to ethylene dichloride : $\lambda_{\text{max.}}$, 288 mμ.; $\varepsilon_{\text{max.}}$, 9740; $\lambda_{\text{min.}}$, 249 mμ.; $\varepsilon_{\text{min.}}$, 572. The origin of the addition complex is therefore not attributable to any form of enhanced dipole association (cf. Hunter, Qureishy, and Samuel, *J.*, 1936, 1576) and it seems probable that this is a further example of the "clathrate" compounds described by Powell (*J.*, 1948, 61).

A molecular model of the 4-ring polymer based on accepted van der Waals radii showed that an ethylene dichloride molecule could be inserted under the more compact configuration of the polymer. This may also explain the ease of crystallisation from ethylene dichloride in the form of the addition complex in contrast to the difficulty experienced with other solvents.

The properties of the pentacyclic polymer (III; $n = 3$) obtained by condensation of the tricyclic *bishydroxymethyl* derivative (V) with *p*-cresol do not agree with those described by Koebner (*Angew. Chem.*, 1933, **46**, 251) for the " pure " substance obtained by treating 4-methyl-2 : 6-bishydroxymethylphenol with 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane ; no analysis was, however, given by him. The ultra-violet absorption spectrum of our specimen, which was purified by " molecular " distillation and gave satisfactory analytical data, therefore provides confirmation of its constitution.

It may be noted that the ultra-violet absorption spectrum of the tricyclic polymer (III; $n = 1$) also fails to support the inherently improbable formula suggested by Niederl and McCoy (*J. Amer. Chem. Soc.*, 1943, **65**, 629) for this compound.

EXPERIMENTAL.

Materials [*with* A. T. CARPENTER].—The specimens of *o*- and *p*-cresol, *m*-4- and *m*-2-xylenol were obtained from the Chemical Research Laboratory, Teddington. *o*- and *p*-Cresol were further purified by distillation under reduced pressure at room temperature (*ca.* 1 mm.), and the *m*-2-xylenol was subjected to 5 recrystallisations from light petroleum (b. p. 80—100°). In view of the low extinction coefficient of the latter ($\lambda_{\text{max.}} = 273$ mμ; $\varepsilon_{\text{max.}} = 1460$), a new and larger specimen was prepared from *m*-2-xylidine as follows. *m*-2-Xylidine (15 g.) in dilute sulphuric acid (15 g. in 450 c.c. of water) was cooled and gradually treated with sodium nitrite (10 g. in 20 c.c. of water). The mixture was heated on a steam-bath until evolution of nitrogen ceased and then distilled in steam, and the distillate was extracted with light petroleum (b. p. 40—60°) [yield 60% (crude)]. After several recrystallisations from light petroleum, *m*-2-xylenol was obtained in needles which had m. p. 47—48° after prolonged drying in a vacuum. The extinction coefficient of this specimen was only slightly higher than that of the original ($\lambda_{\text{max.}} = 274$ mμ.; $\varepsilon_{\text{max.}} = 1500$). The 2 : 2′-, 2 : 4′-, and 4 : 4′-dihydroxydiphenylmethane had m. p. 118—119·5°, 118—119°, and 162—163° respectively. The tricyclic polymer (III; $n = 1$) was prepared as described by Koebner (*loc. cit.*) and had m. p. 212—214°.

Tetracyclic Polymer.—Attempts to prepare this from 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane and formaldehyde in acetic acid following Koebner, and also from a 10 : 1 mixture of these reactants in the presence of hydrochloric acid, led to unsatisfactory results. It was finally prepared by condensation of 2 : 2′-dihydroxy-5 : 5′-dimethyl-3 : 3′-bishydroxymethyldiphenylmethane (m. p. 146—147·5°) with excess of *p*-cresol as follows. A mixture of the dialcohol (10 g.), *p*-cresol (88 g.), and concentrated hydrochloric acid (8 c.c.) was heated on a water-bath for 2 hours, distilled in steam to remove excess of cresol, and dissolved in benzene (200 c.c.), and the crude polymer (9·7 g.; m. p. 172—178°) precipitated with light petroleum. The mother-liquors furnished a further 0·9 g. (m. p. 173—177°), the total yield being 65%. On recrystallisation from ethylene dichloride, the addition *complex* was obtained in hexagonal plates, m. p. 177—179° (Found: C, 69·7; H, 6·3; Cl, 13·2. $C_{31}H_{32}O_4,C_2H_4Cl_2$ requires C, 68·9; H, 6·3; Cl, 12·5%). The polymer was obtained from this by recrystallisation from benzene and heating of the product (m. p. 177—179° after sintering at 176°) in the " molecular " still at 170°. This specimen, which was used for the spectroscopical measurements, melted at 185—188° (Found: C, 80·2; H, 6·9. Calc. for $C_{31}H_{32}O_4$: C, 79·5; H, 6·8%). When the addition complex was heated in the " molecular " still at 170°, the loss in weight corresponded approx. to the loss of a molecular proportion of ethylene dichloride. Microscopic examination of the product showed that this had the same crystal habit as the complex but that the crystals had become opaque.

Pentacyclic Polymer.—An attempt to prepare this from 4-methyl-2 : 6-bishydroxymethylphenol and 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane in glacial acetic acid in the presence of alcoholic hydrochloric acid following the directions of Koebner gave only a resinous product, which became brown but was unmelted at 260°. It is difficult to see how Koebner's preparation could lead to substantial amounts of the pentacyclic polymer since the proportions of reactants would be expected to give rise to a tricyclic derivative with a free active position available for further self-condensation. The pentacyclic polymer was finally prepared as follows. A mixture of the tricyclic bishydroxymethyl derivative (Zinke and Hanus, *Ber.*, 1941, **74**, 205) (5·25 g.), *p*-cresol (40 g.), and concentrated hydrochloric acid (5 c.c.) was heated on a water-bath for 2 hours (whereafter absence of free *o*-hydroxymethyl groups was inferred from the ferric chloride test), and excess of cresol removed by distillation in steam. The white amorphous material thus obtained was dissolved in benzene and precipitated with light petroleum. The product (6·5 g.) could not be crystallised from the usual solvents and was therefore purified by molecular distillation, after being subjected to preliminary degassing at 110°. The pentacyclic *polymer* distilled at 170—190°, furnishing a substance which sintered at 94—104° and melted at 112° [Found: C, 79·2; H, 6·7; *M* (Rast), 564, 569. $C_{39}H_{40}O_5$ requires: C, 79·6; H, 6·8; *M*, 588].

The 4 : 4′-dihydroxydiphenylethane was prepared by Clemmensen reduction of anisoin and subsequent demethylation (Richardson and Reid, *J. Amer. Chem. Soc.*, 1940, **72**, 413) and had m. p. 198—199°.

Spectroscopic Measurements.—The spectroscopic determinations were carried out on ethyl-alcoholic solutions of the compounds. The absorption curves were first plotted from measurements made by the photographic technique, using an iron–nickel arc and a sector photometer. All the quantitative determinations of maxima and minima were checked using fresh solutions on the Beckman photo-electric instrument with 1-cm. layers of alcoholic solution.

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RESEARCH and DEVELOPMENT DEPARTMENT,
BAKELITE LTD., TYSELEY, BIRMINGHAM, 11.
UNIVERSITY OF LIVERPOOL.

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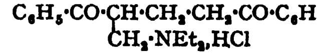
89. *Antituberculous Compounds. Part IV. Compounds related to Diethyl-ω-aryloxyalkylamines.*

By D. A. Peak and T. I. Watkins.

A series of compounds related to the active diethyl-ω-aryloxyalkylamines (I; X = O) (Part I; *J.*, 1949, 2680) has been prepared in which X = S, SO, SO_2, NH, NAlkyl, CO, CH_2, CO·O, or O·CO, *n* = 1 or 2, and Ar = trihalogenophenyl, phenyl, or naphthyl. In addition, the effect of interpolating a phenylene- or a phenyleneoxy-group [cf. V; X = $C_6H_4(\text{-}p)$ or $O\cdot C_6H_4(\text{-}p)$] next to the terminal amino-group was tried in a few cases. Although high *in vitro* activities were obtained in certain cases, no *in vivo* activity could be demonstrated.

Part I of this series (*loc. cit.*) dealt with the effect on the activity against *Mycobacterium tuberculosis* of such structural features of diethyl-ω-aryloxyalkylamines (I; X = O) as the number and position of halogen substituents in the aryl nucleus, the chain length *n*, and the replacement of the terminal diethylamino-group by other basic groups. As no evidence was available about the contribution of the ether linkage to the activity of these compounds, it was though of interest to investigate compounds in which the oxygen atom was replaced by other atoms or groups. This paper describes the preparation of a number of such compounds. Wherever practicable, compounds halogenated in the aryl nucleus were prepared since, although such substitution in the aryloxy-series generally resulted in an increased activity only in the absence of serum, two cases had been observed where this increased activity had been maintained in the presence of serum (Part I, *loc. cit.*). The compounds prepared are listed in the accompanying table, together with the results of biological tests, further details of which will be published elsewhere. In the following discussion the numbers in parentheses following the names of compounds refer to the numbers of the compounds in the table. For convenience, compounds are referred to as the free bases although in most cases they were isolated as their water-soluble hydrochlorides or as Reineckates which were converted into aqueous solutions of the hydrochlorides for test.

(I.) $Ar\cdot X\cdot[CH_2]_n\cdot NEt_2$



$C_6H_5\cdot CO\cdot \underset{CH_2\cdot NEt_2,HCl}{CH}\cdot CH_2\cdot CH_2\cdot CO\cdot C_6H_5$ (II.)

As a first step, the effect of replacing the oxygen atom by a sulphur atom, or a sulphinyl or sulphonyl group was investigated. 2 : 4 : 6-Trichlorophenyl 2-diethylaminoethyl sulphide (1), sulphoxide (2), and sulphone (3) were prepared by conventional methods from the *sodium* salt 2 : 4 : 6-trichlorothiophenol. The sulphone could not be prepared from 2 : 4 : 6-*trichlorobenzenesulphinic acid*, the sodium salt of which failed to condense with diethylaminoethyl chloride. It will be seen that, while the sulphide corresponds very closely in activity to its oxygen analogue (Part I), the activity is reduced in the case of the sulphoxide and is of a very low order in the case of the sulphone.

Nitrogen analogues were prepared by the direct chlorination of *N*-2-diethylaminoethylanilines (I; *n* = 2, X = NR where R = H or alkyl) in acetic acid solution. This led to the formation of trichloro-derivatives (5, 7, 10) when the group attached to the nitrogen atom was small (R = H, Me, and $CH_2\cdot CH_2\cdot NEt_2$). With a larger alkyl group attached to the nitrogen, as in the case of the *N*-octyl and N-*cetyl* (12) compounds, dichloro-derivatives (11, 13) were produced, accompanied by considerable quantities of non-basic tars, presumably formed by fission of the side-chain. Three of these compounds (5, 7, 11) showed high activity in the absence of serum. In the only case (compound 5) where the activity was maintained sufficiently in the presence of serum to justify an *in vivo* test, no effect could be observed on the course of experimental tuberculosis in guinea pigs. Direct iodination and thiocyanation of *N*-methyl-*N*-2-diethylaminoethylaniline afforded *p*-iodo-*N*-methyl-*N*-2-diethylaminoethylaniline (8) and the *p*-thiocyanato-analogue (9) respectively, neither of which showed increased activity in comparison with the parent compound. *N*-2′-Diethylaminoethyl-1- and -2-naphthylamines (14, 15) showed low activity. In these cases direct chlorination led to extensive decomposition, and chloro-derivatives could not be prepared by this method. The orientation of the halogen atoms and the thiocyanato-group in all the foregoing compounds was not proved but the assigned positions were inferred by analogy with the behaviour of simple derivatives of aniline.

Diethyl-2-benzoylethylamine (16) showed a reduced activity in comparison with the oxygen analogue, diethyl-2-phenoxyethylamine (Part I). This compound (16) was prepared by the Mannich condensation of acetophenone with paraformaldehyde and diethylammonium chloride according to the method of Blicke and Burckhalter (*J. Amer. Chem. Soc.*, 1942, **64**, 451). The low yield in this reaction is ascribable, at least in part, to the simultaneous formation of major quantities of a *substance*, probably diethyl-2 : 4-dibenzoylbutylammonium chloride (II), resulting from the condensation of two molecules each of acetophenone and formaldehyde with one of diethylammonium chloride. Attempts to prepare the 2 : 4 : 6-trichloro-derivative of compound (16) by several methods failed. Thus, 1 : 3 : 5-trichloro-2-iodobenzene formed a normal Grignard compound but this failed to react with 2-diethylaminoethyl cyanide. 2 : 4 : 6-Trichlorophenyl cyanide did not react with methylmagnesium iodide, but 2 : 4 : 6-*trichloroacetophenone* was readily prepared from 2 : 4 : 6-trichlorobenzoyl chloride and dimethylcadmium. This acetophenone was devoid of ketonic properties and could not be induced to undergo the Mannich reaction with formaldehyde and diethylammonium chloride, presumably owing to the reduction of the cationoid properties of the carbonyl group by the chlorine atoms. Steric factors probably played little part in this inactivation, since 2 : 3 : 5-*trichloroacetophenone* displayed a similar inertness. Finally, diethyl-2-*m*-aminobenzoylethylamine (17) was prepared by a Mannich condensation of *m*-benzamidoacetophenone with paraformaldehyde and diethylammonium chloride and hydrolysis of the resulting diethyl-2-*m*-benzamidobenzoylethylamine. It was hoped that this compound would yield by chlorination diethyl-2-(2 : 4 : 6-trichloro-3-aminobenzoyl)ethylamine and thence by deamination the required diethyl-2-(2 : 4 : 6-trichlorobenzoyl)ethylamine. Chlorination, however, led to non-basic gums, indicating degradation of the side-chain.

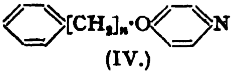
Compound.	Structure. (R = $\cdot[CH_2]_2\cdot NEt_2$.)	Activity.* In absence of serum.	In presence of 10% serum.
(1) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphide	2 : 4 : 6-$C_6H_2Cl_3\cdot S\cdot R$	100 (500)	10
(2) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphoxide	2 : 4 : 6-$C_6H_2Cl_3\cdot SO\cdot R$	50	—
(3) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphone	2 : 4 : 6-$C_6H_2Cl_3\cdot SO_2\cdot R$	5 (10)	—
(4) *N*-2-Diethylaminoethylaniline	$C_6H_5\cdot NHR$	—	1
(5) 2 : 4 : 6-*Trichloro*-N-*2′-diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3\cdot NHR$	100—500	50
(6) *N*-Methyl-*N*-2-diethylaminoethylaniline	$C_6H_5\cdot NMeR$	10	1—5
(7) 2 : 4 : 6-*Trichloro*-N-*methyl*-N-*2′-diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3\cdot NMeR$	500—1000 (5000)	10—50
(8) *p*-Iodo-*N*-methyl-*N*-2-diethylaminoethylaniline	*p*-$I\cdot C_6H_4\cdot NMeR$	10	—
(9) *p*-Thiocyanato-*N*-methyl-*N*-2-diethylaminoethylaniline	*p*-$NCS\cdot C_6H_4\cdot NMeR$	10	—
(10) 2 : 4 : 6-*Trichloro*-NN-*bis-2′-diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3\cdot NR_2$	10	10
(11) 2 : 4-Dichloro-*N*-2′-diethylaminoethyl-*N*-octylaniline	2 : 4-$C_6H_3Cl_2\cdot N(C_8H_{17})\cdot R$	1000	10
(12) N-2-*Diethylaminoethyl*-N-*hexadecylaniline*	$C_6H_5\cdot N(C_{16}H_{33})\cdot R$	1—5	—
(13) 2 : 4-Dichloro-*N*-2′-diethylaminoethyl-*N*-hexadecylaniline	2 : 4-$C_6H_3Cl_2\cdot N(C_{16}H_{33})\cdot R$	5 (50)	—
(14) *N*-2′-Diethylaminoethyl-1-naphthylamine	α-$C_{10}H_7\cdot NHR$	—	1 (10)
(15) *N*-2′-Diethylaminoethyl-2-naphthylamine	β-$C_{10}H_7\cdot NHR$	—	10 (50)
(16) Diethyl-2-benzoylethylamine	$C_6H_5\cdot CO\cdot R$	5	—
(17) Diethyl-2-*m*-aminobenzoylethylamine	*m*-$NH_2\cdot C_6H_4\cdot CO\cdot R$	1	<1
(18) Diethyl-3-phenylpropylamine	$C_6H_5\cdot CH_2R$	50—100	10—50
(19) 2′-Diethylaminoethyl 2 : 4 : 6-trichlorobenzoate	2 : 4 : 6-$C_6H_2Cl_3\cdot CO\cdot OR$	1—5	—
(20) 2′-Diethylaminoethyl 2 : 3 : 5-tri-iodobenzoate	2 : 3 : 5-$C_6H_2I_3\cdot CO\cdot OR$	10	1
(21) 2 : 4 : 6-Trichlorophenyl diethylaminoacetate	2 : 4 : 6-$C_6H_2Cl_3\cdot O\cdot CO\cdot CH_2\cdot NEt_2$	10	5—10
(22) *Phenyl* p-*aminobenzyl ether*	$C_6H_5\cdot O\cdot CH_2\cdot C_6H_4\cdot NH_2$-*p*	—	1—5
(23) 1-*Phenoxy*-2-p-*aminophenoxyethane*	$C_6H_5\cdot O\cdot CH_2\cdot CH_2\cdot O\cdot C_6H_4\cdot NH_2$-*p*	50—500	10
(24) 1-*Phenoxy*-2-(p-*diethylaminophenoxy*)*ethane*	$C_6H_5\cdot O\cdot CH_2\cdot CH_2\cdot O\cdot C_6H_4\cdot NEt_2$-*p*	500	50—100
(25) 1-(2 : 4 : 6-*Trichlorophenoxy*)-2-p-*aminophenoxyethane*	2 : 4 : 6-$C_6H_2Cl_3\cdot O\cdot CH_2\cdot CH_2\cdot O\cdot C_6H_4\cdot NH_2$-*p*	—	—

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Figures in parentheses represent dilutions at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

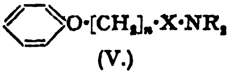
Catalytic reduction of diethyl-2-benzoylethylamine furnished the methylene analogue, diethyl-3-phenylpropylamine (18). This showed increased activity in comparison with diethyl-2-phenoxyethylamine in the absence of serum, but reduced activity in the presence of serum together with high toxicity precluded *in vivo* activity.

$CH_2{:}CH{\cdot}NEt_2,HCl$

(III.)



(IV.)



(V.)

Compounds were also prepared in which the oxygen atom of (I; X = O) was replaced by ester groups of the type (–CO·O–) and (–O·CO–). 2′-Diethylaminoethyl 2 : 4 : 6-trichlorobenzoate (19) and 2 : 3 : 5-tri-iodobenzoate (20) were prepared from 2-diethylaminoethanol and the corresponding acid chlorides. In the former case considerable quantities of a by-product were obtained, apparently identical with diethylvinylammonium chloride (III), obtained by Ladenburg (*Ber.*, 1882, **15**, 1148) by the action of hydrogen iodide on diethylaminoethanol and conversion of the product into the chloride. It is presumably formed here by the elimination of the elements of 2 : 4 : 6-trichlorobenzoic acid from the ester. 2 : 4 : 6-Trichlorophenyl diethylaminoacetate (21) was prepared by the condensation of 2 : 4 : 6-trichlorophenol and diethylaminoacetyl chloride hydrochloride. It could not be prepared from 2 : 4 : 6-*trichlorophenyl chloroacetate* which with diethylamine underwent rapid fission to give *diethylammonium* 2 : 4 : 6-*trichlorophenoxide*. None of the compounds (19, 20, 21) showed high activity.

Finally, in view of the activity of compounds of type (IV) (Barry, O'Rourke, and Twomey, *Nature*, 1947, **160**, 800), it was thought of interest to prepare a few compounds of the type [V; n = 1 or 2, R = H or Et, X = $C_6H_4(\text{-}p)$ or $O{\cdot}C_6H_4(\text{-}p)$]. *Phenyl* p-*aminobenzyl ether* (22), prepared from the corresponding nitro-compound by reduction with aluminium amalgam, was an unstable compound as shown by its ready hydrogenolysis by other reducing agents and the formation of phenol in cold solutions of its *hydrochloride*. Chloro-derivatives were therefore not prepared. 1-*Phenoxy*-2-p-*aminophenoxyethane* (23), prepared by the reduction of 1-phenoxy-2-*p*-nitrophenoxyethane (Ryan and Kenny, *Sci. Proc. Roy. Dublin Soc.*, 1924, **17**, 305), had high activity only in the absence of serum. Ethylation gave 1-*phenoxy*-2-(p-*diethylaminophenoxy*)-*ethane* (24), the high activity of which was less affected by serum. No *in vivo* activity could, however, be demonstrated. Although 1-phenoxy-2-*p*-aminophenoxyethane was of normal basic strength, 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*aminophenoxyethane* (24), prepared by similar methods, was, unexpectedly, a very weak base, the *hydrochloride* and *lactate* of which were extensively hydrolysed by water and activity determinations were not carried out.

EXPERIMENTAL.

2 : 4 : 6-*Trichlorobenzenesulphinic Acid.*—2 : 4 : 6-Trichloroaniline (5 g.) was added at 30° to a solution of sodium nitrite (1·8 g.) in concentrated sulphuric acid (100 c.c.). The solution was then cooled and crushed ice (150 g.) added in portions at 5—8°. A small quantity of tar was removed from the surface, and the clear red solution was saturated at 3—5° with sulphur dioxide. A paste of copper powder (45 g.) and water was then added and the mixture stirred for 3 hours, the temperature being raised to 40° towards the end. The product was isolated as the ferric salt by the method of Thomas (*J.*, 1909, **95**, 342) except that, to avoid separation of the insoluble sulphinic acid, the ferric chloride was added to the filtrate before the addition of the ammoniacal extract of the copper powder. The orange precipitate was filtered off, washed with ethanol to remove coloured impurities, and decomposed with dilute ammonia. Filtration, acidification, and extraction with ether gave 2 : 4 : 6-*trichlorobenzenesulphinic acid* as a colourless solid, m. p. 115° (Found : S, 13·6. $C_6H_3O_2Cl_3S$ requires S, 13·0%). Attempts to condense the sodium salt with diethylaminoethyl chloride in ethanol, methanol, or benzene failed, the sulphinic acid being recovered unchanged.

Sodium Salt of 2 : 4 : 6-*Trichlorothiophenol.*—2 : 4 : 6-Trichloroaniline (5 g.) was diazotised by the method of Hodgson and Mahadevan (*J.*, 1947, 173), the dry diazonium sulphate (8·5 g.) dissolved in ice-water (100 c.c.), and a solution of potassium xanthate (4·5 g.) in ice-water (100 c.c.) added. The yellow, turbid solution was allowed to attain room temperature slowly overnight. (It was found that, if the mixture was allowed to reach room temperature immediately, the temperature rose and a violent reaction occurred.) The heavy brown oil (4·9 g.) was isolated with ether and refluxed for 45 minutes under nitrogen with a solution of potassium hydroxide (0·8 g.) in ethanol (50 c.c.). The solution was then evaporated *in vacuo* and the brown residue dissolved in water and shaken with ether to remove disulphide. The aqueous layer was acidified with acetic acid and extracted with ether, and the ethereal extract washed with water and dried. Titration of the solution with concentrated ethanolic sodium ethoxide until alkaline to phenolphthalein afforded a precipitate of the *sodium* salt of 2 : 4 : 6-trichlorothiophenol, obtained as a colourless solid (1·9 g.) after filtration and washing with ether (Found : S, 13·55; Na, 9·8. $C_6H_2Cl_3SNa$ requires S, 13·5; Na, 9·7%).

2 : 4 : 6-*Trichlorophenyl* 2′-*Diethylaminoethyl Sulphide Hydrochloride.*—The above sodium salt (3·7 g.) was refluxed with diethylaminoethyl chloride (2·1 g.) in absolute ethanol (60 c.c.) under nitrogen for 30 minutes. The mixture was evaporated to dryness *in vacuo* and the residue extracted with ether.

The ethereal solution was extracted with dilute hydrochloric acid, and the crude base liberated with alkali and extracted into ether. Addition of ethereal hydrogen chloride to the dried solution afforded 2 : 4 : ***6-trichlorophenyl 2′-diethylaminoethyl sulphide hydrochloride*** (2·2 g.), long prisms (from ethanol–ether), m. p. 183° (Found: N, 4·0. $C_{12}H_{17}NCl_4S$ requires N, 4·0%).

2 : 4 : 6-*Trichlorophenyl 2′-Diethylaminoethyl Sulphoxide.*—The free base from the foregoing hydrochloride (1·78 g.) was dissolved in glacial acetic acid (10 c.c.), and hydrogen peroxide (100 vol.; 0·8 c.c.; 1·3 mols.) added gradually at 10—15°. The mixture was kept overnight at room temperature and then evaporated *in vacuo.* The crude sulphoxide, liberated with dilute aqueous ammonia, was extracted into ether. Addition of ethereal picric acid afforded the *picrate* (1·81 g.), flat yellow needles (from absolute ethanol), m. p. 140° (Found: C, 39·0; H, 3·4; N, 10·2. $C_{18}H_{19}O_8N_4Cl_3S$ requires C, 38·75; H, 3·4; N, 10·0%). For test the picrate was converted into the free base with lithium hydroxide and dissolved in an equivalent of dilute hydrochloric acid.

2 : 4 : 6-*Trichlorophenyl 2′-Diethylaminoethyl Sulphone Hydrochloride.*—The free base from the sulphide hydrochloride (2·0 g.) was dissolved in 50% acetic acid (10 c.c.), and a solution of potassium permanganate (2·2 g.) in 50% acetic acid (74 c.c.) added at 0—3° during 1 hour. After a further 30 minutes at 5°, the mixture was decolourised with sulphur dioxide and evaporated to dryness *in vacuo.* The crude sulphone, liberated with aqueous ammonia, was extracted with ether. Addition of ethereal picric acid afforded the *picrate* (2·1 g.), flat needles (from ethanol), m. p. 145° (Found: C, 38·1; H, 3·0; N, 10·0. $C_{18}H_{19}O_9N_4Cl_3S$ requires C, 37·6; H, 3·3; N, 9·8%). The free base, obtained from the picrate with lithium hydroxide, was neutralised with ethanolic hydrogen chloride. Evaporation afforded the *hydrochloride,* colourless needles (from ethanol–ether), m. p. 170° (Found: N, 3·8. $C_{12}H_{17}O_2NCl_4S$ requires N, 3·7%).

N-2-*Diethylaminoethylaniline and* NN-*Bis*-(2-*diethylaminoethyl*)*aniline.*—Aniline (93 g.), diethylaminoethyl chloride hydrochloride (172 g.), and powdered anhydrous sodium carbonate (106 g.) were mixed and heated on the steam-bath for 8 hours by which time evolution of carbon dioxide had ceased. The mixture was diluted with water and made slightly alkaline to Titan-yellow with aqueous sodium hydroxide, and the oil separated, dried, and fractionated. After a forerun of aniline (18 g.), *N*-2-diethylaminoethylaniline (108 g.; b. p. 110—114°/1·8 mm.) was collected (Dewar, *J.*, 1944, 622, gives b. p. 162—164°/25 mm.) and finally a third fraction, b. p. 115—155°/1·8 mm. (32 g.). Repeated fractionation of the last fraction through an 8″ Vigreux column gave pure *N*-bis-(2-diethylaminoethyl)aniline (8·6 g.), b. p. 146—148°/1·2 mm. (Found: N, 14·3. Calc. for $C_{18}H_{33}N_3$: N, 14·4%) (Stahmann and Cope, *J. Amer. Chem. Soc.*, 1946, **68**, 2494, give b. p. 174—177°/6 mm.). The *dipicrate* crystallised from ethoxyethanol in yellow plates, m. p. 170—170·5° (Found: C, 48·3; H, 5·1; N, 16·9. $C_{30}H_{39}O_{14}N_9$ requires C, 48·1; H, 5·2; N, 16·8%).

2 : 4 : 6-*Trichloro*-N-2′-*diethylaminoethylaniline.*—Chlorine was passed into a mixture of *N*-2-diethylaminoethylaniline (10 g.) and glacial acetic acid (100 c.c.) at 20° until the gain in weight was 11·1 g. (= 3 mols. of chlorine). Water (200 c.c.) was added, and the solution neutralised with solid sodium carbonate and finally made alkaline to Titan-yellow with sodium hydroxide. The liberated oil was isolated with ether and distilled, the fraction of b. p. 145—150°/1·5 mm. (7·2 g.) being collected. The redistilled product (6·2 g.; b. p. 157—158°/2·5 mm.) was converted into the *picrate,* which after repeated crystallisation from methanol (yellow rhomboidal plates) had m. p. 150—151° (6·4 g.) (Found: N, 13·6. $C_{18}H_{20}O_7N_5Cl_3$ requires N, 13·3%). Reconversion of the picrate into the free base gave 2 : 4 : 6-*trichloro*-N-2′-*diethylaminoethylaniline* as a colourless liquid (2·72 g.), b. p. 150—152°/2 mm. (Found: N, 9·9. $C_{12}H_{17}N_2Cl_3$ requires N, 9·5%).

2 : 4 : 6-*Trichloro*-NN-*bis*-(2′-*diethylaminoethyl*)*aniline.*—*NN*-Bis-(2-diethylaminoethyl)aniline (8·0 g.), chlorinated similarly, gave much tar and a fraction (2·8 g.), b. p. 168—178°/2 mm. Purified through the *dipicrate,* yellow prisms (from ethoxyethanol), m. p. 206—207° after sintering at 204° (Found: N, 15·0. $C_{30}H_{36}O_{14}N_9Cl_3$ requires N, 14·8%), this afforded 2 : 4 : 6-*trichloro*-NN-*bis*-(2′-*diethylaminoethyl*)-*aniline* as a colourless liquid (1·04 g.), b. p. 170°/1·8 mm. (Found: N, 11·0. $C_{18}H_{30}N_3Cl_3$ requires N, 10·65%).

2 : 4 : 6-*Trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline.*—*N*-Methyl-*N*-2-diethylaminoethylaniline, prepared by the method used for *N*-2-diethylaminoethylaniline, had b. p. 124—125°/3 mm. (Dewar, *loc. cit.*, gives b. p. 165—170°/20 mm.). This material (10 g.), chlorinated in acetic acid, afforded a fraction, b. p. 148—152°/2·5 mm. (11·6 g.). Purified through the *picrate* (4·7 g.), m. p. 149—150° after repeated crystallisation from methanol (rhomboidal plates) (Found: N, 13·4. $C_{19}H_{22}O_7N_5Cl_3$ requires N, 13·0%), this gave 2 : 4 : 6-*trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline* as a colourless liquid (1·7 g.), b. p. 142°/1 mm. (Found: N, 9·3. $C_{13}H_{19}N_2Cl_3$ requires N, 9·05%).

p-*Iodo*-N-*methyl*-N-2′-*diethylaminoethylaniline Hydrochloride.*—*N*-Methyl-*N*-2′-diethylaminoethylaniline (32·2 g.) was dissolved in concentrated hydrochloric acid (1 l.), and an excess (115 g., 4·5 mols.) of iodine monochloride in concentrated hydrochloric acid (300 c.c.) added. An oil separated which gradually formed greenish-yellow crystals when kept. The product (76 g.) was a complex of the desired compound with iodine monochloride. It dissolved readily in acetone (500 c.c.), the solution rapidly depositing a greyish-white solid (42 g.). The mother-liquor became dark and lachrymatory, probably owing to the formation of iodoacetone. Crystallisation from methanol–acetone afforded needles of p-*iodo*-N-*methyl*-N-2′-*diethylaminoethylaniline hydrochloride* (24 g.) in a solvated form, m. p. 135—140° (decomp.). When heated at 100° for some hours this lost 15% by weight and then crystallised from acetone in prisms, m. p. 168—169° (Found: C, 42·9; H, 6·0; N, 8·0. $C_{13}H_{22}N_2ClI$ requires C, 42·3; H, 6·0; N, 7·6%). Neither form could be converted into the other by seeding. They both afforded the same picrate, red needles m. p. 141—142°. Reconversion of the picrate into the hydrochloride *via* the free base afforded the solvated form irrespective of the origin of the picrate.

p-*Thiocyanato*-N-*methyl*-N-2′-*diethylaminoethylaniline Hydrochloride.*—To *N*-methyl-*N*-2′-diethylaminoethylaniline (5·1 g.) in carbon tetrachloride (10 c.c.) was added a solution of thiocyanogen in carbon tetrachloride (1·1 mols.; Wood and Fieser, *J. Amer. Chem. Soc.*, 1941, **63**, 2327). The solution became warm and the red oil which separated soon solidified. Recrystallisation from ethanol and aqueous methanol afforded the water-insoluble p-*thiocyanato*-N-2′-*diethylaminoethylaniline monothiocyanate* as almost colourless needles, m. p. 95—96° (Found: N, 17·4. $C_{18}H_{22}N_4S_2$ requires N, 17·4%). The *picrate* separated from methanol in red needles, m. p. 125° (Found: N, 17·2. $C_{20}H_{24}O_7N_6S$ requires N, 17·2%). The free base was obtained by dissolving the crude thiocyanate (4·7 g.) in warm ethanol, adding an excess of 5N-hydrochloric acid, followed by an excess of dilute aqueous sodium carbonate, and isolating the resulting oil (2·8 g.) with ether. The *hydrochloride* separated from ethanol–ether in compact prisms (1·7 g.), m. p. 147—147·5° (Found: N, 14·1. $C_{14}H_{22}N_3ClS$ requires N, 14·0%).

2 : 4-*Dichloro*-N-2′-*diethylaminoethyl*-N-*octylaniline*.—*N*-2-Diethylaminoethylaniline (20 g.), octyl bromide (20 g.), and anhydrous potassium carbonate (20 g.) were heated at 150—160° for 7 hours. Water was then added, and the mixture made strongly alkaline to Titan-yellow and extracted with ether. The aqueous layer and a dark interface layer of quaternary hydroxide were discarded and the ether layer was concentrated. The residue afforded on distillation *N*-2′-diethylaminoethyl-*N*-octylaniline as a colourless oil (16·25 g.), b. p. 175—180°/2 mm. It was characterised as its *dipicrate*, yellow prisms (from methanol or ether), m. p. 82—83° (Found: N, 14·9. $C_{32}H_{42}O_{14}N_8$ requires N, 14·7%). Chlorination in acetic acid gave much tar and a fraction (8·1 g.), b. p. 188—195°/1·8 mm. Conversion into the Reineckate and repeated crystallisation from methanol afforded 2 : 4-*dichloro*-N-2′-*diethylaminoethyl*-N-*octylaniline Reineckate* as red plates, m. p. 140—142° (Found: C, 42·1; H, 5·85; N, 15·8; Cl, 11·1. $C_{24}H_{41}N_8Cl_2S_4Cr$ requires C, 41·5; H, 5·9; N, 16·2; Cl, 10·3%). The substance therefore probably contained some trichlorinated material. For test the Reineckate was converted into the hydrochloride with silver chloride in methanol, the methanol removed *in vacuo*, and the residue dissolved in water.

2 : 4-*Dichloro*-N-2′-*diethylaminoethyl*-N-*hexadecylaniline*.—In the same way N-2-*diethylaminoethyl*-N-*hexadecylaniline* was obtained in 50·5% yield as a colourless liquid, b. p. 238—244°/1·8 mm. and b. p. 239—242°/1·8 mm. on redistillation (Found: N, 6·9. $C_{28}H_{52}N_2$ requires N, 6·7%). Its *Reineckate* crystallised from methanol in red prisms, m. p. 135—136° (Found: N, 15·2. $C_{32}H_{59}N_8S_4Cr$ requires N, 15·2%). Chlorination of this material (20·8 g.) and fractionation of the product gave the dichloro-derivative as a colourless oil (9·6 g.), b. p. 246—250°/0·8 mm. It was purified as the *Reineckate*, red plates (from methanol), m. p. 131—132° (Found: C, 48·0; H, 7·2; N, 13·6; Cl, 8·4. $C_{32}H_{57}N_8Cl_2S_4Cr$ requires C, 47·8; H, 7·1; N, 13·9; Cl, 8·8%), and converted as above into the hydrochloride for testing.

N-2′-*Diethylaminoethyl*-1- and -2-*naphthylamines*.—Condensation of 1-naphthylamine (72 g.) and diethylaminoethyl chloride hydrochloride (86 g.) in the usual way afforded *N*-2′-diethylaminoethyl-1-naphthylamine as a colourless liquid (60·7 g.), b. p. 160—162°/0·8 mm. (Stahmann and Cope, *loc. cit.*, record b. p. 156—157°/1 mm.). Its *dipicrate* crystallised from ethanol in red prisms, m. p. 154—155° (Found: N, 16·3. $C_{28}H_{28}O_{14}N_8$ requires N, 16·0%). Its *dihydrochloride* separated from chloroform in tacky crystals, m. p. <100°, probably containing chloroform of crystallisation. Trituration with hot acetone yielded colourless crystals, m. p. 158—160° (Found: N, 9·2. $C_{16}H_{24}N_2Cl_2$ requires N, 8·9%). It gave a solution of low pH which could be adjusted to pH 5 without precipitation of the base. *N*-2′-Diethylaminoethyl-2-naphthylamine was prepared in similar yield as a colourless liquid with a strong blue fluorescence, b. p. 195°/3·5 mm. Its *monopicrate* separated from ethanol or acetic acid in yellow prisms, m. p. 152—153° (Found: N, 14·7. $C_{22}H_{25}O_7N_5$ requires N, 14·8%). For test the picrate was reconverted into the free base and dissolved in one equivalent of N-sulphuric acid. Attempted chlorination of both of these bases led to extensive decomposition and tar formation.

Diethyl-2-benzoylethylammonium Chloride.—Following the directions of Blicke and Burckhalter (*loc. cit.*), acetophenone (12 g.), diethylammonium chloride (11 g.), and paraformaldehyde (3·6 g.) were heated under reflux in absolute ethanol (20 c.c.) for 3 hours. The solution was filtered, the ethanol removed *in vacuo*, and the residue dissolved in water (50 c.c.). The free base was isolated by basification and extraction with ether. The ethereal solution was evaporated *in vacuo* and the residual oil kept over sulphuric acid *in vacuo* for 2 days to remove traces of diethylamine. (Failure to do this gave a low-melting final product very difficult to purify.) The oil was redissolved in ether, and the solution saturated with dry hydrogen chloride. The precipitated hydrochloride crystallised from acetone in needles (8·25 g.), m. p. 112—113° (Found: N, 5·85. Calc. for $C_{13}H_{20}ONCl$: N, 5·8%) (Blicke and Burckhalter, *loc. cit.*, give m. p. 108—110°).

In one experiment in which the aqueous solution was made just alkaline to Brilliant-yellow with aqueous sodium carbonate before extraction with ether, the aqueous layer subsequently deposited needles (7·6 g.), m. p. *ca.* 150°. Repeated crystallisation from methanol–ether and from water afforded a *substance*, probably diethyl-(2 : 4-dibenzoylbutyl)ammonium chloride, m. p. 193—194° after drying at 100° (Found: C, 70·5; H, 7·5; N, 3·8. $C_{22}H_{28}O_2NCl$ requires C, 70·6; H, 7·5; N, 3·75%).

Diethyl-3-phenylpropylammonium Chloride.—Diethyl-2-benzoylethylammonium chloride (9·6 g.) was hydrogenated with palladised charcoal (10%; 4 g.). Hydrogenation was rapid at 50°/atmospheric pressure, nearly the theoretical for 2 moles of hydrogen being absorbed. The catalyst was filtered off and the ethanol removed *in vacuo*. The residue, which partly crystallised, was triturated with acetone, and the crystals were separated. Crystallisation from acetone afforded diethyl-3-phenylpropylammonium chloride as non-hygroscopic colourless plates (3·2 g.), m. p. 117—118° (Found: N, 6·3. Calc. for $C_{13}H_{22}NCl$: N, 6·15%) (Mannich and Chang, *Ber.*, 1933, **66**, *B*, 418, describe it as a hygroscopic substance, m. p. 119—120°). The free base had b. p. 118°/13 mm. (Found: N, 7·55. Calc. for $C_{13}H_{21}N$: N, 7·3%) (von Braun, *Ber.*, 1910, **43**, 3217, records b. p. 137—139°/22 mm.).

Attempted Reaction between 2 : 4 : 6-*Trichlorophenylmagnesium Bromide and* 2-*Diethylaminoethyl Cyanide*.—A Grignard solution was prepared from 1 : 3 : 5-trichloro-2-iodobenzene (3·95 g., 1 mol.; prepared by the method of Hodgson and Mahadevan, *loc. cit.*) and magnesium (0·42 g., 1½ mols.) in ether (50 c.c.), with ethyl bromide (0·5 g., ½ mol.) as entrainer. A solution of 2-diethylaminoethyl cyanide (2·1 g., 1½ mols.) was then added and the mixture refluxed for 30 minutes. After decomposition with ice and hydrochloric acid, the ethereal layer afforded 1 : 3 : 5-trichlorobenzene (2·2 g., 91%), m. p. 60° undepressed by admixture with authentic 1 : 3 : 5-trichlorobenzene, indicating at least 91% formation of trichlorophenylmagnesium iodide and practically no reaction of the latter with the diethylaminoethyl cyanide. The acid layer yielded only small quantities of basic ketonic material. Similar results were obtained when refluxing was continued for 24 hours or when the reaction was carried out in boiling toluene or anisole. In the latter solvent some 2 : 2′ : 4 : 4′ : 6 : 6′-hexachlorodiphenyl, plates (from acetic acid), m. p. 112·5°, was isolated.

2 : 4 : 6- *and* 2 : 3 : 5-*Trichloroacetophenone*.—2 : 4 : 6-Trichlorophenyl cyanide (Meyer and Sudborough, *Ber.*, 1894, **27**, 3152) failed to react with methylmagnesium iodide in ether or anisole. Accordingly 2 : 4 : 6-trichlorobenzoyl chloride (11·5 g., 1 mol.) in benzene (50 c.c.) was added to a solution of dimethylcadmium (4 mols.) in benzene (prepared in the usual manner from methylmagnesium bromide and cadmium chloride). The mixture was heated under reflux for 3 hours and then decomposed with ice and hydrochloric acid, and the benzene layer washed with water, dried (Na_2SO_4), and concentrated. Fractionation of the residue afforded 2 : 4 : 6-*trichloroacetophenone* as a colourless liquid (6·8 g., 65%), b. p. 138—142°/7 mm., which quickly solidified and then had m. p. 60° (Found: C, 42·6; H, 2·6. $C_8H_5OCl_3$ requires C, 43·0; H, 2·2%). The substance did not form a 2 : 4-dinitrophenylhydrazone. Attempted condensation with dimethylammonium chloride and paraformaldehyde in acetic acid (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206), *iso*amyl alcohol (Kamp and Mossettig, *J. Amer. Chem. Soc.*, 1936, **58**, 1568), or nitrobenzene (Fry, *J. Org. Chem.*, 1945, **10**, 259) failed to yield any Mannich base, and 2 : 4 : 6-trichloroacetophenone was recovered unchanged. 2 : 3 : 5-Trichloroacetophenone, b. p. 120°/1 mm. (Found: C, 44·0; H, 2·8. $C_8H_5OCl_3$ requires C, 43·0; H, 2·3%), was prepared similarly in poor yield (20%), the major product being a *substance*, needles (from chloroform), m. p. 230° (Found: C, 41·6; H, 1·8%).

Diethyl-2-(m-*aminobenzoyl*)*ethylammonium Chloride*.—*m*-Aminoacetophenone (95·5 g.) and benzoic anhydride (160 g.) were heated at 100° for 20 minutes. The crude product was boiled with successive quantities of 3% aqueous sodium carbonate until the supernatant solution no longer gave a precipitate of benzoic acid on acidification. The residue was washed with water, dried, and crystallised from light petroleum (b. p. 80—100°), affording *m*-benzamidoacetophenone as needles, m. p. 108° (170 g.). This was stirred with diethylammonium chloride (85·7 g., 1·1 mols.), paraformaldehyde (32 g., 1·5 mols.), and concentrated hydrochloric acid (2 c.c.) in a mixture of benzene (300 c.c.) and nitrobenzene (300 c.c.) (cf. Fry, *loc. cit.*) and heated for 2 hours (oil-bath, 110—115°). A water-entrainer was now incorporated in the apparatus, the oil-bath heated to 145—150°, and water (29 c.c.) collected during 1 hour. The mixture on cooling deposited a thick crop of needles. Recrystallisation from absolute ethanol afforded *diethyl*-2-(m-*benzamidobenzoyl*)*ethylammonium chloride* (154·5 g.) as needles, m. p. 142° (Found: N, 7·6. $C_{20}H_{25}O_2N_2Cl$ requires N, 7·8%). Evaporation of the benzene–nitrobenzene mother-liquor and crystallisation of the residue from ethanol–ether gave a further crop (14·5 g.), m. p. 137—138°. The combined crops (169 g.) were heated under reflux for 6 hours with concentrated hydrochloric acid (1400 c.c.). The solution was cooled and the benzoic acid filtered off. The filtrate was extracted with ether and concentrated *in vacuo* to 150 c.c. On cooling, *diethyl*-2-(m-*aminobenzoyl*)*ethylammonium chloride* separated in needles (100·5 g.), m. p. 185° unaltered by further crystallisation (Found: N, 9·5. $C_{13}H_{22}ON_2Cl_2$ requires N, 9·5%). A further crop (19 g., m. p. 183—184°) was obtained by evaporation of the mother-liquor *in vacuo* to dryness and crystallisation of the residue from ethanol. Attempted chlorination of this product led in all cases to non-basic gums.

2-*Diethylaminoethyl* 2 : 4 : 6-*Trichlorobenzoate Hydrochloride*.—2 : 4 : 6-Trichlorobenzoyl chloride (3 g.) (Sudborough, *J.*, 1894, **65**, 1030; 1895, **67**, 602) was added to diethylaminoethanol (1·6 g.) in pure chloroform (8 c.c.) and, after 3 hours at room temperature, the mixture was warmed to 40° for 7 hours. Precipitation with ether and fractional crystallisation of the crystalline product from benzene–ethanol afforded two compounds. The first, m. p. 133—134·5° (Found: N, 10·3. Calc. for $C_6H_{14}NCl$: N, 10·3%), afforded an aurichloride, plates (from hot water), m. p. 138°. Ladenburg (*loc. cit.*) records no properties for diethylvinylammonium chloride but states that the aurichloride has m. p. 138—140°. The compound is therefore distinct from the normal polymerisation product of diethylaminoethyl chloride, tetraethylpiperazinium dichloride, which has the same empirical formula but does not melt below 300° and gives a diaurichloride of m. p. 236—237° (Slotta and Behnisch, *Annalen*, 1932, **497**, 170). The second compound was dissolved in water and then basified with aqueous sodium hydroxide, and the resultant oil isolated with ether. Reconversion into the hydrochloride gave 2-*diethylaminoethyl* 2 : 4 : 6-*trichlorobenzoate hydrochloride* (0·3 g.), needles (from ethanol–ether), m. p. 193° (Found: N, 4·15. $C_{13}H_{17}O_2NCl_4$ requires N, 3·9%).

2-*Diethylaminoethyl* 2 : 3 : 5-*Tri-iodobenzoate Hydrochloride*.—2 : 3 : 5-Tri-iodobenzoic acid (5·0 g.) (Wheeler and Johns, *Amer. Chem. J.*, 1910, **43**, 407) was refluxed with thionyl chloride (3 c.c.) and benzene (15 c.c.) until a clear solution was obtained. The benzene and excess of thionyl chloride were evaporated *in vacuo*, the yellow crystalline residue was dissolved in pure chloroform (15 c.c.), and 2-diethylaminoethanol (1·3 g., 10% excess) added. Cooling overnight in the ice-chest gave 2-*diethylaminoethyl* 2 : 3 : 5-*tri-iodobenzoate hydrochloride* as a pale yellow solid (4·2 g.), m. p. *ca.* 180° after softening at 165°. Recrystallisation from chloroform–acetone and finally from ethanol gave the substance as colourless prisms (2·35 g.), m. p. 184—185° (Found: N, 2·4. $C_{13}H_{17}O_2NClI_3$ requires N, 2·2%).

2 : 4 : 6-*Trichlorophenyl Diethylaminoacetate Hydrochloride*.—(a) *Attempted preparation from* 2 : 4 : 6-*trichlorophenyl chloroacetate*. 2 : 4 : 6-Trichlorophenol (9·9 g.) was heated at 100° with excess of chloroacetyl chloride for 48 hours. Evolution of hydrogen chloride was slow and evidently incomplete. The mixture was poured into water and made faintly alkaline to Brilliant-yellow, and the solid filtered off. Recrystallisation from methanol gave 2 : 4 : 6-*trichlorophenyl chloroacetate* (3·8 g.), m. p. 69—70° unchanged by further crystallisation (Found: C, 34·6; H, 1·6. $C_8H_4O_2Cl_4$ requires C, 35·0; H, 1·5%). This substance (1·28 g.) was dissolved in dry ether (15 c.c.), and diethylamine (1·0 c.c.) added. Large prisms soon separated. The product (0·80 g.) recrystallised from ethanol in prisms, m. p. 157—159° (Found: N, 5·2. $C_{10}H_{14}ONCl_3$ requires N, 5·2%). It dissolved in dilute alkali to give free diethylamine and, on acidification, trichlorophenol. It was therefore *diethylammonium* 2 : 4 : 6-*trichlorophenoxide*.

(b) *From diethylaminoacetyl chloride and* 2 : 4 : 6-*trichlorophenol*. Chloroacetic acid (94·5 g., 1 mol.) was mixed with crushed ice, and diethylamine (219 g., 3 mols.) added portion-wise. The mixture was set aside at room temperature for 60 hours. It was then evaporated on the steam-bath after the addition of 5N-sodium hydroxide (400 c.c., 2 mol.-equivs.) until the smell of diethylamine had disappeared. The solution was then made strongly acid to Congo-red and evaporated to a thick syrup. The syrup was taken up in ethanol, filtered from sodium chloride, and again evaporated. The residue partly crystallised on storage in a desiccator over sulphuric acid. Oil was removed by trituration with methanol–acetone (1 : 4). The residue (61 g.) was extracted with methanol (50 c.c.) and filtered. Dilution of the filtrate with acetone (200 c.c.) gave *diethylaminoacetic acid hydrochloride* (32 g.) as large prisms, m. p. 125—126°. A further crop (7·0 g.; m. p. 125—126°) was obtained by re-extraction of the insoluble residue with methanol (15 c.c.) and precipitation with acetone (60 c.c.). The material so obtained was slightly hygroscopic. Recrystallisation from methanol–acetone gave non-hygroscopic material, m. p. 125—126° (Found : N, 8·35. $C_6H_{14}O_2NCl$ requires N, 8·35%).

The foregoing salt (3·0 g.) was finely ground, dried at 100°, and refluxed with thionyl chloride (2 c.c.) in dry chloroform (15 c.c.) until the solid just dissolved (20 minutes). Chloroform and excess of thionyl chloride were removed *in vacuo*, the residual light-brown solid redissolved in chloroform, and 2 : 4 : 6-trichlorophenol (2·5 g.) added. The solution was cooled in ice-water, and pyridine (2 c.c.) added dropwise. After 4 hours, the chloroform was removed *in vacuo*, and the residue dissolved in water (10 c.c.) and acidified to pH 2 with concentrated hydrochloric acid. Unchanged trichlorophenol was extracted with ether, the aqueous layer basified with solid sodium hydrogen carbonate to pH 8—9, and the resulting oil isolated with ether. After removal of the last traces of pyridine *in vacuo* over sulphuric acid, the residual dark-red mobile liquid was dissolved in ether, and a slight excess of ethanolic hydrogen chloride added. The resulting 2 : 4 : 6-*trichlorophenyl diethylaminoacetate hydrochloride* (3·3 g.) crystallised from acetone in colourless prisms, m. p. 148° (decomp.) (Found : N, 4·2. $C_{12}H_{15}O_2NCl_4$ requires N, 4·0%).

Phenyl p-*Aminobenzyl Ether Hydrochloride*.—Phenyl *p*-nitrobenzyl ether (4 g.; m. p. 94—95°) (Kumpf, *Annalen*, 1884, **224**, 104, gives m. p. 91°), dissolved in wet ether (80 c.c.), was reduced with amalgamated aluminium (4 g.), water (12 c.c.) being added portion-wise at such a rate as to maintain vigorous reaction. After 24 hours, the ether was filtered from the sludge of alumina, and the product precipitated as the hydrochloride by the addition of ethanolic hydrogen chloride (5 c.c. of 4·5N.). The crude product (4 g.) decomposed on attempted crystallisation from methanol, phenol being liberated. It was therefore shaken with ether and excess of dilute aqueous sodium hydroxide, the ether evaporated, and the residue (2·4 g.) crystallised from benzene–light petroleum. *Phenyl* p-*aminobenzyl ether* separated in needles (1·62 g.), m. p. 78—78·5° (Found : N, 7·2. $C_{13}H_{13}ON$ requires N, 7·0%). Precipitation of its ethereal solution with ethanolic hydrogen chloride gave the *hydrochloride* as a white powder, m. p. 140—145° (decomp.) (Found : N, 5·85. $C_{13}H_{14}ONCl$ requires N, 5·9%). It dissolved in water to give a slightly turbid solution which developed the smell of phenol when kept. Other methods of reduction of the nitro-compound, *e.g.*, neutral iron, stannous chloride, or ammoniacal ferrous sulphate, caused fission of the molecule.

1-*Phenoxy*-2-p-*aminophenoxyethane*.—1-Phenoxy-2-*p*-nitrophenoxyethane was prepared by the condensation of potassium *p*-nitrophenoxide (45 g.) and 2-phenoxyethyl bromide (50·8 g.) in boiling butanol (228 c.c.) for 40 hours. The reaction mixture was filtered hot. The product (53 g.) separated, on cooling, in needles, m. p. 87—88°. A sample recrystallised from ethanol to constant m. p. had m. p. 90° (Found : N, 5·4. Calc. for $C_{14}H_{13}O_4N$: N, 5·4%). Ryan and Kenny (*loc. cit.*) give m. p. 86°. The nitro-compound (53 g.) was heated under reflux for 24 hours with a solution of hydrated sodium sulphide (98·5 g.) and sulphur (13·1 g.) in 50% ethanol (103 c.c.). The solid which separated on cooling was filtered off, washed, and dissolved in warm benzene (400 c.c.). The benzene solution was washed first with water and then shaken with 5N-hydrochloric acid (100 c.c.), and the insoluble 1-*phenoxy*-2-p-*aminophenoxyethane hydrochloride* (46 g.; m. p. 206—208°) filtered off and washed with benzene. Recrystallisation from dilute hydrochloric acid gave the pure substance as needles, m. p. 210° (Found : N, 5·6. $C_{14}H_{16}O_2NCl$ requires N, 5·3%). The free *base* (39 g.) was obtained by warming the crude hydrochloride with a mixture of benzene (500 c.c.) and N-sodium carbonate solution (550 c.c.) until all went into solution, separating the benzene layer, and evaporating it *in vacuo*. A portion, crystallised twice from ethanol, had m. p. 109—110° (Found : N, 6·55. $C_{14}H_{15}O_2N$ requires N, 6·1%). The *hemipicrate* crystallised from benzene in yellow plates, m. p. 158° (Found : N, 10·2. $C_{34}H_{33}O_{11}N_5$ requires N, 10·2%).

1-*Phenoxy*-2-p-*diethylaminophenoxyethane*.—The foregoing base (5·25 g.) was heated and stirred under reflux with acetone (100 c.c.), ethyl iodide (4·1 c.c., 2·1 mols.), and potassium carbonate (6·4 g.) for 20 hours. The acetone was evaporated, water added to the residue, and the oil extraced with ether. The ethereal extract was filtered from flocculent, insoluble material, dried (Na_2SO_4), and evaporated. The residual oil (5·7 g.), which partly solidified when kept, was dissolved in a hot solution of picric acid (5·7 g.) in ethanol (100 c.c.). On cooling, 1-*phenoxy*-2-(p-*diethylaminophenoxy*)*ethane picrate* (8·25 g.) separated in yellow plates, m. p. 135—137° raised to 137—138° by recrystallisation (Found : C, 55·5; H, 5·5; N, 11·1. $C_{24}H_{26}O_9N_4$ requires C, 56·1; H, 5·1; N, 10·9%). This was shaken with aqueous lithium hydroxide and ether, and the ethereal solution separated and evaporated. The residual oil (4·3 g.), crystallised from methanol (10 c.c.) at 0°, furnished the free *base*, m. p. 40—41° (Found : N, 5·05. $C_{18}H_{23}O_2N$ requires N, 4·9%). For test the substance was dissolved in an equivalent of dilute hydrochloric acid to give a solution of pH 5.

1-(2 : 4 : 6-*Trichlorophenoxy*)-2-p-*aminophenoxyethane*.—2 : 4 : 6-Trichlorophenol (15 g.) was dissolved in ethanol (100 c.c.), and a solution of sodium hydroxide (3·1 g.) in water (10 c.c.) added. The solution was then heated under reflux with ethylene dibromide (30 g.) for 30 hours. The ethanol was evaporated *in vacuo*, and the crystalline residue isolated with ether and distilled. 2-(2 : 4 : 6-*Trichlorophenoxy*)*ethyl bromide* was obtained as a colourless liquid (15·4 g.), b. p. 184—185°/3 mm., which soon solidified. Crystallisation of a small portion from ethanol afforded long needles, m. p. 49—50° (Found : C, 31·6; H, 2·2. $C_8H_6OCl_3Br$ requires C, 31·5; H, 2·0%).

The foregoing compound (14·8 g.) was added to a suspension of sodium *p*-nitrophenoxide formed by adding sodium hydroxide (2·0 g.) in water (5 c.c.) to a solution of *p*-nitrophenol (6·8 g.) in ethanol (100 c.c.). The mixture was heated under reflux for 20 hours, only a part of the solid having by then dissolved. The ethanol was evaporated *in vacuo* and the residue extracted with benzene. The benzene extract was shaken with dilute sodium hydroxide and evaporated, the residue solidifying on cooling. Crystallisation from ethanol (50 c.c.) afforded crude 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*nitrophenoxyethane* (10·4 g.), m. p.

80—100°, contaminated with unchanged trichlorophenoxyethyl bromide. Recrystallisation of a small portion from methanol gave needles, m. p. 116—116·5° (Found : N, 4·4. $C_{14}H_{10}O_4NCl_3$ requires N, 3·9%). The crude product (8·5 g.) was reduced as previously with amalgamated aluminium (8·5 g.) in ether (340 c.c.), and ethanolic hydrogen chloride added to the ethereal filtrate. The precipitated crude hydrochloride was reconverted into the free base. Crystallisation from light petroleum–benzene gave 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*aminophenoxyethane* (2·6 g.) as needles, m. p. 77—78° (Found : N, 4·3. $C_{14}H_{12}O_2NCl_3$ requires N, 4·2%). The *hydrochloride* crystallised from 2N-hydrochloric acid or methanol in rosettes of needles, m. p. 237—239° (Found : N, 3·7. $C_{14}H_{13}O_2NCl_4$ requires N, 3·8%). The *lactate* similarly crystallised from aqueous lactic acid in needles, m. p. 143—144° (Found : N, 3·5. $C_{17}H_{18}O_5NCl_3$ requires N, 3·3%).

Both salts were largely hydrolysed in solution, giving turbid solutions of pH 2 which deposited free base on cooling.

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Research Laboratories, Boots Pure Drug Co. Ltd.,
Nottingham.
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90. *Antituberculous Compounds. Part V. 2-Sulphanilamido-5-alkyl-1 : 3 : 4-oxadiazoles and -thiadiazoles and Related* iso*Thiosemicarbazones and* iso*Thioureas.*

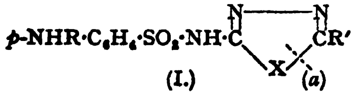
By J. D. Brooks, P. T. Charlton, P. E. Macey, D. A. Peak, and W. F. Short.

Following the observation of the specific *in vitro* activity, against *Mycobacterium tuberculosis*, of 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole (I; X = O, R = H, R′ = Me), a number of derivatives and analogues of this compound have been prepared. These include N^4-acyl derivatives and higher alkyl homologues (R′ = amyl, undecyl, and heptadecyl). Similar activity is shown by corresponding thiadiazoles (I; X = S).

Structurally analogous *iso*thiosemicarbazones have also been prepared. Although these were generally active *in vitro*, a selected compound showed no activity *in vivo* in contrast to the closely related, therapeutically active benzaldehyde thiosemicarbazones (Domagk, *Nordisk Medicin*, 1948, **39**, 1322).

A series of *iso*thioureas has also been prepared. *N*-Aryl*iso*thioureas showed high *in vitro* activity only in the absence of serum. Cyclic *iso*thioureas, such as 2-aminobenzthiazoles and 2-alkylthiopyrimidines, were without interest.

The work to be described in the present paper arose from the observation made in 1944 that 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole (I; X = O, R = H, R′ = Me), while virtually inactive against organisms normally sensitive to sulphonamides, exhibited a highly specific activity *in vitro* against *Mycobacterium tuberculosis*. The compound, first prepared in 1943, has since been described (Tappi and Migliardi, *Arch. Sci. Biol.*, 1941, **27**, 170; Tappi, *Rec. Trav. chim.*, 1943, **62**, 207; not available in abstract form in this country until 1944), but without reference to its antituberculous activity. Complete inhibition of the growth of *M. tuberculosis* occurs at dilutions of 1 in 10,000—50,000, 4-aminosalicylic acid showing the same activity under the same conditions of test. Although this activity is of a comparatively low order, the low toxicity of the compound and its apparent persistence in high concentrations in the blood-stream gave promise of chemotherapeutic activity. An extensive series of *in vivo* tests failed to indicate any such activity, and this inactivity was later accounted for by the demonstration that the Bratton–Marshall estimation of blood-levels is misleading in this case, the compound being in fact rapidly metabolised to an inactive substance. Details of this work will be published elsewhere.



(I.)

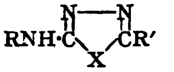
$$p\text{-}NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot C(XR){:}N\cdot N{:}CR'R''$$

(II.)

Before the explanation of this negative result was obtained, derivatives and homologues had been prepared in order to elucidate the structural features of activity and in the hope of increasing the activity. The compounds prepared are summarised in Table I, together with their *in vitro* activities. In the subsequent discussion figures in parentheses following the name of a compound refer to the number of the compound in this or other tables.

TABLE I.

*5-Amino-2-alkyl-*1 : 3 : 4*-oxadiazoles and -thiadiazoles.*



	Compound. -1 : 3 : 4-oxadiazole or -thiadiazole.	X.	R′.	R″.	M. p.	Formula.	Found N, %.	Req. N, %.	Activity * in absence of serum.
(1)	2-Sulphanilamido-5-methyl-	O	Me	$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	175°	$C_9H_{10}O_3N_4S$	21·5	22·0	10—50
(2)	2-(3 : 5-*Di-iodosulphanilamido*)*-5-methyl-*	O	Me	$NH_2{\cdot}C_6H_2I_2{\cdot}SO_2{\cdot}$	228—229	$C_9H_8O_3N_4I_2S$	11·3	11·1	1
(3)	2-N^4-Acetylsulphanilamido-5-methyl-	O	Me	$AcNH{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	212	$C_{11}H_{12}O_4N_4S$	—	—	<1
(4)	2-N^4-*Hexoylsulphanilamido-5-methyl-*	O	Me	$C_5H_{11}{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	203	$C_{15}H_{20}O_4N_4S$	15·9	15·9	5
(5)	2-N^4-*Dodecoylsulphanilamido-5-methyl-*	O	Me	$C_{11}H_{23}{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	124	$C_{21}H_{32}O_4N_4S$	12·7	12·8	5
(6)	2-N^4-*Stearoylsulphanilamido-5-methyl-*	O	Me	$C_{17}H_{35}{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	128—129	$C_{27}H_{44}O_4N_4S$	10·7	10·8	1
(7)	2-*Toluene-*p*-sulphonamido-5-methyl-*	O	Me	$CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	152	$C_{10}H_{11}O_3N_3S$	16·7	16·6	1
(8)	2-*Amino-5-amyl-*	O	C_5H_{11}	H	151	$C_7H_{13}ON_3$	27·2	27·1	1
(9)	2-*Amino-5-undecyl-*	O	$C_{11}H_{23}$	H	150—151	$C_{13}H_{25}ON_3$	17·3	17·6	1
(10)	2-*Amino-5-heptadecyl-*	O	$C_{17}H_{35}$	H	143	$C_{19}H_{37}ON_3$	13·5, 13·3	13·0	<1
(11)	2-N^4-*Acetylsulphanilamido-5-amyl-*	O	C_5H_{11}	$AcNH{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	186	$C_{15}H_{20}O_4N_4S$	15·9	15·9	1
(12)	2-N^4-*Acetylsulphanilamido-5-amyl-*	S	C_5H_{11}	$AcNH{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	201—202	$C_{15}H_{20}O_3N_4S_2$	15·3	15·2	1
(13)	2-*Sulphanilamido-5-amyl-*	O	C_5H_{11}	$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	148—149	$C_{13}H_{18}O_3N_4S$	18·3	18·1	50
(14)	2-*Sulphanilamido-5-amyl-*	S	C_5H_{11}	$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	182	$C_{13}H_{18}O_2N_4S_2$	17·4	17·2	50
(15)	2-*Sulphanilamido-5-undecyl-*	O	$C_{11}H_{23}$	$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	105—107	$C_{19}H_{30}O_3N_4S$	14·1	14·2	100
(16)	2-*Sulphanilamido-5-heptadecyl-*	O	$C_{17}H_{35}$	$NH_2{\cdot}C_6H_4{\cdot}SO_2{\cdot}$	91—93	$C_{25}H_{42}O_3N_4S$	11·4	11·7	10

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

(1) Preparation by Dr. H. Kitchen. Found : C, 42·55; H, 4·4. Calc. for $C_9H_{10}O_3N_4S$: C, 42·5; H, 4·0%. Tappi and Migliardi (*loc. cit.*) and Tappi (*loc. cit.*) record m. p. 172°. (3) Found : S, 10·6. Calc. for $C_{11}H_{12}O_4N_4S$: S, 10·8%. Tappi (*loc. cit.*) records m. p. 213°. (4), (5), (6), and (7) Preparations by Dr. R. P. Hullin. (8) Colourless needles by precipitation of its solution in hydrochloric acid with dilute ammonia solution.

2-N^4-*Hexoyl-, -dodecoyl-,* and *-stearoyl-sulphanilamido-5-methyl-*1 : 3 : 4-*oxadiazoles* (4, 5, 6) were prepared by conventional methods from 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole. The activity was in all cases lower than that of the parent compound and the N^4-acetyl derivative (3) was completely inactive, indicating the necessity for a free N^4-amino-group. This was further shown by the low activity of 2-*toluene*-p-*sulphonamido-5-methyl*-1 : 3 : 4-*oxadiazole* (7), prepared from 2-amino-5-methyl-1 : 3 : 4-oxadiazole (Stollé and Fehrenbach, *J. pr. Chem.*, 1929, **122**, 289; De, *J. Indian Chem. Soc.*, 1930, **7**, 651) and toluene-*p*-sulphonyl chloride. Iodination of the 2-sulphanilamido-compound with iodine monochloride afforded a *di-iodo*-derivative (2) of low activity, again possibly due to the weakened basicity of the N^4-amino-group.

The homologous series, 2-*amino-5-amyl-, -undecyl-,* and *-heptadecyl*-1 : 3 : 4-*oxadiazoles* (8, 9, 10), was prepared from the corresponding 1-acylthiosemicarbazides by the action of lead monoxide in boiling ethanol (cf. Stollé and Fehrenbach, *loc. cit.*). The yields were progressively poorer in the case of the higher homologues, particularly the heptadecyl compound for which cyclisation was retarded by the formation of an insoluble lead salt of the 1-stearoylthiosemicarbazide. All three compounds were of low activity. Their *sulphanilyl* derivatives (13, 15, 16), prepared by conventional methods, showed activity which was of a high order in the case of the undecyl compound. No *in vivo* tests were carried out in view of the realisation at this time of the rapid inactivation of the methyl homologue in the blood-stream. One thiadiazole was prepared. 1-Hexoylthiosemicarbazide was cyclised with benzenesulphonic acid to 2-*amino-5-amyl*-1 : 3 : 4-*thiadiazole* and thence converted into the N^4-*acetylsulphanilyl* and *sulphanilyl* derivatives (12, 14). The last-named showed the same activity as its oxygen analogue; its acetyl derivative exhibited the same weak activity as 2-N^4-*acetylsulphanilamido-5-amyl*-1 : 3 : 4-*oxadiazole* (11).

In view of the unfavourable *in vivo* properties of this series, modifications of the structure were sought. A possible line of approach appeared to be the preparation of uncyclised forms of the molecule in which fission may be regarded to have taken place at the bond (*a*) in (I). This would lead to 4-sulphanilyl-3-alkyl*iso*semicarbazones (II; X = O, R = alkyl, R′ and R″ = H or alkyl) from the oxadiazoles and to 4-sulphanilyl-3-alkyl*iso*thiosemicarbazones (II; X = S, R = alkyl, R′ and R″ = H or alkyl) from the thiadiazoles. *In vitro* tests with 2-sulphanilamido-5-methyl-1 : 3 : 4-thiadiazole (I; X = S, R = H, R′ = Me), a supply of which was kindly made available to us by the Therapeutic Research Corporation of Great Britain Ltd., had shown that it possessed activity similar to that of the oxadiazole and that it was subject to the same *in vivo* limitations. Results with the amyl homologues (12, 14) confirmed that oxygen and sulphur were interchangeable in the molecule. Since 3-alkyl*iso*thiosemicarbazones were more readily accessible than 3-alkyl*iso*semicarbazones, it was proposed to prepare a series of sulphanilyl derivatives of the former. The first compound prepared, acetone 3-ethyl*iso*thiosemicarbazone (17; Table II) had, itself, fair activity but its 4-*sulphanilyl* derivative (18) was almost completely devoid of activity. Further work was therefore directed towards examination of the 3-alkyl*iso*thiosemicarbazones themselves. These were prepared smoothly in all cases by the method of Baird, Burns, and Wilson (*J.*, 1927, 2527) and their properties and activities are summarised in Table II. Benzaldehyde 3-ethyl*iso*thiosemicarbazone (19) was as active as the acetone analogue and, in a series of 3-alkyl homologues, high activity was reached with the butyl derivative (20), falling to zero with the hexadecyl derivative (22). The butyl derivative was not seriously affected by serum but no *in vivo* activity could be demonstrated in guinea-pigs. No favourable effect was produced by the introduction of a 3-(2-diethylaminoethyl) group (23) or of a 4-phenyl or 4-*p*-butoxyphenyl group (24, 25, 26).

Late in 1946, the first information regarding parallel work which had been proceeding in Germany became available in this country. Behnisch (*Elberfeld Ann. Res. Reports*, No. 17, p. 2; FD 20/46) reported the activity of various substituted benzaldehyde thiosemicarbazones. In particular, *p*-pyrrolidino- and *o*-nitro-benzaldehyde thiosemicarbazones were mentioned as active, the latter having been selected for clinical test. The 3-ethyl*iso*thiosemicarbazones (27, 29) corresponding to these two compounds were therefore prepared together with *p*-dimethylaminobenzaldehyde thiosemicarbazone (28). None of these compounds showed promising activity, nor did *o*-nitrobenzaldehyde thiosemicarbazone itself. This is in agreement with the recent findings of Hoggarth, Martin, Storey, and Young (*Brit. J. Pharmacol.*, 1949, **4**, 248) who found no *in vivo* activity with *o*-nitrobenzaldehyde thiosemicarbazone or with 3-alkyl*iso*thiosemicarbazones in general. Subsequent publications (Domagk, Behnisch, Mietzsch, and Schmidt, *Naturwiss.*, 1946, **33**, 15; Domagk, *Zentr. Gynäk.*, 1947, **69**, 833) show that their approach to the thiosemicarbazones was almost identical with our own, starting in their case from the observation of the activity of 2-sulphanilamido-5-ethyl-1 : 3 : 4-thiadiazole (I; X = S,

TABLE II.

3-*Alkyl*iso*thiosemicarbazones and 2-alkyl*iso*thioureas.*

Compound.	RN:C(SR')·NHR''.			Hydrohalide.				Activity.‡	
	R.	R'.	R''.	M. p.	Formula.	Found N, %.	Req. N, %.	In absence of serum.	In presence of serum.
-*iso**thiosemicarbazone.*									
(17) Acetone 3-ethyl-	$Me_2C{:}N-$	Et	H	153—154°	$C_6H_{13}N_3S,HCl$ *	21·35	21·5	10	10
(18) *Acetone 4-sulphanilyl-3-ethyl-*	$Me_2C{:}N-$	Et	$\cdot SO_2\cdot C_6H_4\cdot NH_2$-*p*	—	—	—	—	1	—
(19) Benzaldehyde 3-ethyl-	$PhCH{:}N-$	Et	H	193—194	$C_{10}H_{13}N_3S,HCl$	17·3	17·2	10	10—50
(20) Benzaldehyde 3-butyl-	$PhCH{:}N-$	C_4H_9	H	185—186	$C_{12}H_{17}N_3S,HCl$ *	15·7	15·5	100 (500)	50
(21) Benzaldehyde 3-octyl-	$PhCH{:}N$	C_8H_{17}	H	176	$C_{16}H_{25}N_3S,HCl$ *	12·8	12·8	10	10
(22) Benzaldehyde 3-hexadecyl-	$PhCH{:}N-$	$C_{16}H_{33}$	H	162—163	$C_{24}H_{41}N_3S,HCl$ *	9·8	9·6	<1	—
(23) Benzaldehyde 3-(2-diethyl-aminoethyl)-	$PhCH{:}N-$	$NEt_2\cdot CH_2\cdot CH_2\cdot$	H	192	$C_{14}H_{22}N_4S,2HCl$ *	15·5	15·95	10	10
(24) *Benzaldehyde 4-phenyl-3-ethyl-*	$PhCH{:}N-$	Et	Ph	—	—	—	—	50 (100)	10
(25) Benzaldehyde 4-phenyl-3-(2-diethylaminoethyl)-	$PhCH{:}N-$	$NEt_2\cdot CH_2\cdot CH_2\cdot$	Ph	—	—	—	—	10	5—10
(26) *Benzaldehyde 4-p-butoxyphenyl-3-ethyl-*	$PhCH{:}N-$	Et	*p*-$C_4H_9O\cdot C_6H_4\cdot$	—	—	—	—	10	—
(27) *p*-Pyrrolidinobenzaldehyde 3-ethyl-	*p*-$[CH_2]_4{>}N\cdot C_6H_4\cdot CH{:}N-$	Et	H	245 †	$C_{14}H_{20}N_4S,HCl$ *	17·7	17·9	(50)	—
(28) *p*-Dimethylaminobenzaldehyde 3-ethyl-	*p*-$Me_2N\cdot C_6H_4\cdot CH{:}N-$	Et	H	230—232	$C_{12}H_{18}N_4S,HCl$ *	19·8	19·5	1	—
(29) *o*-Nitrobenzaldehyde 3-ethyl-	*o*-$NO_2\cdot C_6H_4\cdot CH{:}N-$	Et	H	169·5—170·5	$C_{10}H_{12}O_2N_4S,HCl$ *	19·2	19·4	(10)	—
-*iso**thiourea.*									
(30) *N*-Phenyl-*S*-ethyl-	Ph	Et	H	—	—	—	—	>500	1—5
(31) *N*-Phenyl-*S*-butyl-	Ph	C_4H_9	H	—	—	—	—	100	10 (50)
(32) *N*-Phenyl-*S*-octyl-	Ph	C_8H_{17}	H	—	—	—	—	50	5
(33) *N*-*p*-Butoxyphenyl-*S*-ethyl-	*p*-$C_4H_9O\cdot C_6H_4\cdot$	Et	H	—	—	—	—	1—5	1—5
(34) *NN'*-Diphenyl-*S*-ethyl	Ph	Et	Ph	—	—	—	—	100 (500)	1—5
(35) *S*-Methyl-	H	Et	H	115—117	$C_2H_6N_2S,HI$	—	—	—	<1
(36) *S*-Butyl-	H	C_4H_9	H	109—110	$C_5H_{12}N_2S,HI$ *	11·0	10·8	—	5
(37) *S*-Octyl	H	C_8H_{17}	H	96—96·5	$C_9H_{20}N_2S,HBr$ *	10·85, 10·7	10·4	—	1

* New compound.

† With decomposition.

‡ See Notes to Table I. Figures in parentheses represent dilutions at which partial inhibition occurred.

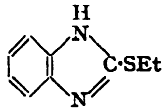
(17) Needles from acetone. (18) See Experimental. (19) Baird *et al.* (*loc. cit.*) record m. p. 195°. (20) Colourless rods from ethanol–acetone. (21) Shining plates from acetone. (22) Needles from acetone–methanol. (23) Hygroscopic plates from acetone–ethanol. (24) The free base crystallised from ethanol in large pale yellow plates, m. p. 78° (Found : N, 14·85. $C_{16}H_{17}N_3S$ requires N, 14·85%). (25) The *Reineckate*, crystallised from 40% acetone, had m. p. 166—167° (decomp.) (Found : N, 20·7. $C_{24}H_{33}N_{10}S_5Cr$ requires N, 20·8%). For test this was converted into an aqueous solution of the hydrochloride. (26) The free *base* crystallised from ethanol in plates, m. p. 90° (Found : N, 12·2. $C_{20}H_{25}ON_3S$ requires N, 11·8%). It was feebly basic. (27) Reddish-brown needles from ethanol. (28) The *dihydrochloride* crystallised from ethanol containing a little hydrogen chloride in yellow needles, m. p. 219—220° (decomp.) (Found : N, 17·85. $C_{12}H_{20}N_4Cl_2S$ requires N, 17·3%), converted into red needles of the monohydrochloride by boiling with ethanol. (29) Irregular crystals from ethanol containing a little hydrogen chloride. (30) The picrate, yellow needles from 70% ethanol, had m. p. 199·5° (Found : N, 17·4. Calc. for $C_{15}H_{15}O_7N_5S$: N, 17·1%). Bertram (*Ber.*, 1892, **25**, 55) records m. p. 196°. (31) The *picrate*, yellow plates from ethanol, had m. p. 144° (Found : N, 16·2. $C_{17}H_{19}O_7N_5S$ requires N, 16·0%). (32) The *picrate*, minute yellow needles from ethanol, had m. p. 130·5° (Found : N, 14·5. $C_{21}H_{27}O_7N_5S$ requires N, 14·2%). (33) The *picrate*, large yellow prisms from ethanol, had m. p. 162—163° (Found : N, 14·9. $C_{19}H_{23}O_8N_5S$ requires N, 14·55%). (34) The free base, crystallised from aqueous ethanol, had m. p. 73° (Found : N, 11·1. Calc. for $C_{15}H_{16}N_2S$: N, 10·95%. Will (*Ber.*, 1881, **14**, 1490) records m. p. 79° and Rathke (*ibid.*, p. 1777) records m. p. 73°. (35) Bernthsen and Klinger (*Ber.*, 1878, **11**, 492) record m. p. 117°. (36) Plates from chloroform. (37) Plates from chloroform–ether.

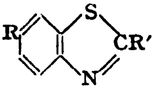
R = H, R′ = Et). It is now clear that, notwithstanding the apparent logic of the approach, the activities of the thiadiazoles and thiosemicarbazones are in fact entirely unrelated. Thus, while the oxa- and thia-diazoles are equally active, semicarbazones, in contrast with the corresponding thiosemicarbazones, are entirely inactive (Behnisch, Mietzsch, and Schmidt, *Angew. Chem.*, 1948, **60**, 113; Hoggarth *et al.*, *loc. cit.*). Further, while the sulphanilamido-group is essential to the activity of the oxa- and thia-diazoles, it greatly reduces the activity in the case of *iso*thiosemicarbazones as noted above. The fact that the *iso*thiosemicarbazones are more closely related structurally to the thiadiazoles than are the thiosemicarbazones is therefore without significance. The latter structure is apparently more favourable in this series to the development of *in vivo* activity, in spite of the approximately equivalent *in vitro* activity of the two types of compound. Our own subsequent trials have confirmed the high *in vivo* activity of selected members of the thiosemicarbazone group (Domagk, *Nordisk Medicin*, 1948, **39**, 1322; Hoggarth *et al.*, *loc. cit.*).

As a further simplification of the basic structure, *S*-alkyl*iso*thioureas, prepared by standard methods, were next examined. Very high *in vitro* activity was shown by *N*-phenyl- and *NN′*-diphenyl-*S*-ethyl*iso*thioureas (30, 34). This was reduced in the former case by substitution of *S*-butyl and *S*-octyl groups (31, 32) for ethyl or by introduction of a *p*-butoxy-group into the *N*-phenyl substituent (33). This series was not extended, since poor activity in the presence of serum precluded *in vivo* activity.

2-Ethylthiobenziminazole (III), which may be regarded as a cyclic *iso*thiourea, was prepared from 2-mercaptobenziminazole (Billeter and Steiner, *Ber.*, 1887, **20**, 231) by interaction with ethyl iodide. It was only weakly active. 2-Aminobenzthiazoles may also be regarded as cyclic *iso*thioureas, and the claims of Freedlander and French (*Proc. Soc. Exp. Biol. Med.*, 1947, **66**, 362) that *in vivo* activity had been demonstrated with such compounds and with related 2-alkoxybenzthiazoles prompted us to examine a selection of these compounds.

(III.)





(IV.)

2 : 6-Diaminobenzthiazole (IV; R = R′ = NH_2), stated to be one of the most active compounds, was prepared by the method of Kaufmann and Schultz (*Arch. Pharm.*, 1935, **273**, 31). It had relatively low *in vitro* activity and no *in vivo* activity. 2-Amino-6-butoxybenzthiazole (IV;

TABLE III.

2-Alkylthiopyrimidines.

Pyrimidine.	B. p.	M. p.	Formula.	Found N, %.	Req. N, %.
(38) 2-Mercapto-4 : 6-dimethyl-	—	209—212°	—	—	—
(39) 2-Methylthio-4 : 6-dimethyl-	113—114°/15 mm.	27—28	$C_7H_{10}N_2S$	18·2	18·2
(40) 2-*Methylthio-4-phenyl-6-methyl-*	154—160°/1 mm.	—	$C_{12}H_{12}N_2S$	13·0	13·0
(41) 4-Hydroxy-2-methylthio-6-methyl-	—	224—225	—	—	—
(42) 4-Hydroxy-2-methylthio-5-methyl-	—	234·5—236	—	—	—
(43) 4-*Hydroxy-2-butylthio-5-methyl-*	—	105—106	$C_9H_{14}ON_2S$	14·5, 14·3	14·1
(44) 4-*Hydroxy-2-octylthio-5-methyl-*	—	88—89	$C_{13}H_{22}ON_2S$	11·1	11·0
(45) 4-Chloro-2-methylthio-6-methyl-	118—120°/12 mm.	34—34·5	—	—	—
(46) 4-*Chloro-2-methylthio-6-methyl-*	132°/15 mm.	20—23	$C_6H_7N_2ClS$	15·9	16·0
(47) 4-*Chloro-2-butylthio-5-methyl-*	124—126°/1 mm.	—	$C_9H_{13}N_2ClS$	12·6	12·9
(48) 4-*Chloro-2-octylthio-5-methyl-*	144—148°/2 mm.	—	$C_{13}H_{21}N_2ClS$	10·5	10·2
(49) 4-Amino-2-methylthio-6-methyl-	—	135—136	—	—	—
(50) 4-*Amino-2-methylthio-5-methyl-*	—	130—131	$C_6H_9N_3S$	27·4	27·1
(51) 4-*Amino-2-butylthio-5-methyl-*	—	85—86	$C_9H_{15}N_3S$	21·5	21·3
(52) 4-*Amino-2-octylthio-5-methyl-*	—	85—86	$C_{13}H_{23}N_3S$	16·7	16·6

(38) Evans (*J. pr. Chem.*, 1893, **48**, 489) records m. p. 210°. (39) Hale and Williams (*J. Amer. Chem. Soc.*, 1915, **37**, 594) record m. p. 24°. Wheeler and Merriam (*Amer. Chem. J.*, 1904, **32**, 356) record m. p. 23—24° and b. p. 123—125°/14 mm. (41) Wheeler and Merriam (*ibid.*, 1903, **29**, 478) record m. p. 219°. (42) *Idem, ibid.*, record m. p. 233°. (43) Rods from ethanol. (44) Rhombic plates from methanol. (45) Wheeler and McFarland (*loc. cit.*) record b. p. 147°/32—35 mm., needles (from light petroleum), m. p. 39—40°. (49) Backer and Grevenstuk (*Rec. Trav. chim.*, 1945, **64**, 115) and Hull, Lovell, Openshaw, and Todd (*J.*, 1947, 41) record 136—137° and 133·5—135° respectively. (50) Clusters of rods from water. (51) Thin plates from benzene. (52) Irregular plates from light petroleum.

R = OBu, R′ = NH$_2$), probably identical with the "*p*-butoxyaminobenzthiazole" described in F.P. 742,398, was prepared by the same procedure and was also devoid of activity. Attempted preparation of 6-amino-2-butoxybenzthiazole by the reduction of 6-*nitro-2-butoxybenzthiazole* with stannous chloride led to simultaneous chlorination with the formation of x-*chloro-6-amino-2-butoxybenzthiazole dihydrochloride*, also quite inactive.

Finally, as a further variant of alkyl*iso*thioureas, a number of substituted 2-alkylthiopyrimidines were prepared. These are summarised in Table III. In the preparation of 2-mercapto-4-phenyl-6-methylpyrimidine (Merkatz, *Ber.*, 1919, **52**, 869) as an intermediate for the 2-*methylthio*-derivative (40), an alkali-insoluble by-product was obtained and identified as *di*-(4-*phenyl*-6-*methyl*-2-*pyrimidyl*) *disulphide*, the same product being produced by oxidation of the mercaptopyrimidine with iodine. Condensation of the appropriate 2-alkyl*iso*thiourea with ethyl α-formylpropionate according to the method of Wheeler and Merriam (*Amer. Chem. J.*, 1903, **29**, 478) afforded 4-hydroxy-2-methylthio-, -2-*butylthio*-, and -2-*octylthio-5-methylpyrimidines* (42, 43, 44). These were converted smoothly into the 4-*chloro*-derivatives (46, 47, 48) by phosphorus pentachloride and phosphorus oxychloride (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431) and thence by ethanolic ammonia into the 4-*amino*-derivatives (50, 51, 52). The corresponding 2-methylthio-6-methylpyrimidines (41, 45, 49) were also prepared. All compounds except the intermediate chloro-derivatives were tested *in vitro*. Activities are not recorded since in no case were the compounds active at a dilution greater than 1 in 1000 in the presence of serum.

EXPERIMENTAL.

N^4-*Acyl Derivatives of* 2-*Sulphanilamido*-5-*methyl*-1 : 3 : 4-*oxadiazole*.—These were prepared by the condensation of 2-sulphanilamido-5-methyl-1 : 3 : 4-oxadiazole with the corresponding acid anhydride in benzene solution in the case of the *hexoyl* derivative, and with the corresponding acid chloride in pyridine solution in the case of the *dodecoyl* and *stearoyl* derivatives. The *toluene*-p-*sulphonyl* derivative was similarly prepared in pyridine. The products were crystallised from ethanol.

2-*Amino*-5-*alkyl*-1 : 3 : 4-*oxadiazoles*.—1-Acylthiosemicarbazides were prepared by heating a mixture of powdered thiosemicarbazide (1 mol.) with the appropriate acid anhydride (1 mol.) at 80° and finally at 110—120°. The product was triturated with ether or ethanol–ether and crystallised from ethanol. This afforded an impure product which was, however, satisfactory for the next stage. The crude acylthiosemicarbazide (10·0 g.) was stirred and heated under reflux with absolute ethanol (150—200 c.c.) and lead monoxide (3 mols.) for 15—30 hours. The lead sulphide and unchanged lead oxide were filtered off, the ethanol was removed *in vacuo*, and the solid residue triturated with aqueous sodium hydroxide to remove unchanged acylthiosemicarbazide. The residue was crystallised from ethanol–ether. In the case of 1-stearoylthiosemicarbazide the yield was poor owing to the formation of an insoluble lead salt of the thiosemicarbazide. Some improvement was effected by conducting the reaction in propanol instead of ethanol.

2-*Sulphanilamido*-5-*alkyl*-1 : 3 : 4-*oxadiazoles*.—The 2-amino-5-alkyloxadiazole was heated with acetylsulphanilyl chloride (1 mol.) in dry pyridine at 100° for 20—45 minutes, and the mixture poured into excess of dilute hydrochloric acid. The crude N^4-acetyl derivative was filtered off and hydrolysed in the usual manner with boiling 2N-sodium hydroxide. The crude product, obtained by acidification with hydrochloric acid, was purified by crystallisation from ethanol or aqueous ethanol.

2-*Sulphanilamido*-5-*amyl*-1 : 3 : 4-*thiadiazole*.—1-Hexoylthiosemicarbazide (22 g.) and benzenesulphonic acid (30 g., 1·25 mols.) were heated on the steam-bath for 15 minutes. The melt was cooled and dissolved in water, and the clear solution basified with ammonia. The precipitated solid was crystallised from ethanol, affording 2-*amino*-5-*amyl*-1 : 3 : 4-*thiadiazole* (17 g.) as needles, m. p. 195° (Found : N, 24·8. $C_7H_{13}N_3S$ requires N, 24·6%). The N^4-*acetylsulphanilyl* and *sulphanilyl* derivatives (see Table I) were prepared by the same methods as for the oxadiazoles and were both crystallised from ethanol.

2-(3 : 5-*Di-iodosulphanilamido*)-5-*methyl*-1 : 3 : 4-*oxadiazole*.—2-Sulphanilamido-5-methyloxadiazole (2·5 g.) was dissolved in water (15 c.c.) and concentrated hydrochloric acid (4 c.c.), and a solution of iodine monochloride (3·3 g.) in concentrated hydrochloric acid (3 c.c.) added. The solution soon became turbid and deposited a dark oil which solidified when warmed and scratched. The solid was filtered off, dried, and crystallised from ethanol. Yield, 3·0 g. (see Table I).

Benzaldehyde 4-p-*Butoxyphenylthiosemicarbazone*.—Following the general method for the preparation of aryl*iso*thiocyanates (*Org. Synth.*, Coll. Vol. I, 1941, p. 448), *p*-butoxyaniline (33 g.) was mixed with carbon disulphide (24 g.) with ice-cooling. Considerable heat was evolved, and the mixture solidified. Ethanol (36 c.c.) was added and after 2 hours the solid was broken up and cooled to 10°. Concentrated aqueous ammonia (33 g.) was then added at 10—15° in small portions with vigorous shaking. The solid dissolved and the ammonium salt of the dithiocarbamate crystallised. After being kept overnight, the crystals were filtered off, washed with ether (2 × 20 c.c.), and dissolved in water (400 c.c.). Addition of a solution of lead nitrate (70 g.) in water (200 c.c.) caused rapid precipitation of lead sulphide. The reaction was completed by boiling and the *p*-butoxyphenyl *iso*thiocyanate (11·25 g., 27%) isolated by extraction with ether as a mobile, odourless oil. The crude product (4·25 g.) in absolute ethanol (6 c.c.) was treated with hydrazine hydrate (1·2 c.c. of 90%) in ethanol (1 c.c.) with cooling. 4-*p*-Butoxyphenylthiosemicarbazide separated immediately in plates (4·2 g.), m. p. 175°. The crude product was heated under reflux for 3 hours with ethanol (60 c.c.) and benzaldehyde (2·2 g.). After filtration from a little undissolved solid, the solution on concentration afforded *benzaldehyde* 4-p-*butoxyphenylthiosemi*-

carbazone (4·5 g.) as pale yellow needles, m. p. 164—165° after recrystallisation from ethanol (Found: N, 12·9. $C_{18}H_{21}ON_3S$ requires N, 12·85%).

3-*Alkyl*iso*thiosemicarbazones.*—These were prepared from the corresponding thiosemicarbazones by alkylation with sodium ethoxide and the appropriate alkyl halide in ethanol (Baird, Burns, and Wilson, *loc. cit.*). The hydrochlorides were formed by precipitation of the crude bases in ether with hydrogen chloride and by crystallisation of the product from a suitable solvent (see Table II).

Acetone 4-N^4-*Acetylsulphanilyl-3-ethyl*iso*thiosemicarbazone.*—Acetone 3-ethyl*iso*thiosemicarbazone (3·2 g.) was stirred with 50% ethanol (25 c.c.) and sodium hydrogen carbonate (2·1 g.), and acetylsulphanilyl chloride (5·13 g., 1·1 mols.) was added at 20°. The viscous oil, which separated on stirring of the mixture overnight, afforded a granular solid on trituration with ether containing a little ethanol. Crystallisation from ethanol yielded crude *acetone* 4-N^4-*acetylsulphanilyl-3-ethyl*iso*thiosemicarbazone* (0·67 g.) as prisms, m. p. 167—168° raised by repeated recrystallisation from ethanol and from acetic acid to 183—184° (Found: N, 15·8. $C_{14}H_{20}O_3N_4S_2$ requires N, 15·7%).

When sodium hydroxide was used instead of sodium hydrogen carbonate the sole product obtained was ethyl acetylsulphanilate, plates (from aqueous ethanol), m. p. 121—122° (Found: N, 5·9. Calc. for $C_{10}H_{11}O_4NS$: N, 5·8%). Crossen, Jenkins, and Rogers (*Pharm. Arch.*, 1941, **12**, 26) quote m. p. 121°. Hydrolysis afforded sulphanilic acid, identified by colour reactions and analysis (Found: N, 8·0. Calc. for $C_6H_7O_3NS$: N, 8·1%).

*Acetone 4-Sulphanilyl-3-ethyl*iso*thiosemicarbazone.*—The foregoing compound (0·17 g.) was heated with 2·5N-sodium hydroxide (1 c.c.) at 100° for 1 hour. Acidification to pH 4 afforded a precipitate of *acetone 4-sulphanilyl-3-ethyl*iso*thiosemicarbazone* (0·14 g.), prisms (from ethanol), m. p. 186—187° (Found: N, 17·9. $C_{12}H_{18}O_2N_4S$ requires N, 17·8%).

N-p-*Butoxyphenylthiourea.*—*p*-Butoxyphenyl *iso*thiocyanate (7·0 g.) in ethanol (20 c.c.) was treated with gaseous ammonia with cooling until no further crystalline material separated. The product (7·5 g.) was crystallised from ethanol, giving N-p-*butoxyphenylthiourea* as rods, m. p. 163° (Found: N, 12·4. $C_{11}H_{16}ON_2S$ requires N, 12·5%).

S-*Alkyl*iso*thioureas.*—These were prepared from the appropriate thiourea and alkyl halide in refluxing ethanol. The resulting alkyl*iso*thiourea hydrohalides were tested as such or converted into picrates and thence into aqueous solutions of the hydrochlorides for test.

2-*Ethylthiobenziminazole.*—2-Mercaptobenziminazole (Billeter and Steiner, *loc. cit.*) (1·5 g.), suspended in ethanol (5 c.c.), was heated under reflux with ethyl iodide (1·6 g.) for 2 hours, complete dissolution occurring after 15 minutes. The ethanol was evaporated *in vacuo* and the crystalline residue (2·88 g.) dissolved in water, the solution filtered, and the free base precipitated with sodium carbonate solution. Recrystallisation of the resulting white solid from aqueous ethanol afforded 2-*ethylthiobenziminazole* as needles, m. p. 173·5—174·5° (Found: N, 15·9. $C_9H_{10}N_2S$ requires N, 15·7%).

2-*Amino-6-butoxybenzthiazole.*[*]—A solution of bromine (10 g.) in glacial acetic acid (13 c.c.) was added slowly with stirring to a solution of *p*-butoxyaniline (8·25 g.) and ammonium thiocyanate (9·5 g.) in 95% acetic acid (50 c.c.). The yellow solid which separated overnight was filtered off and the filtrate diluted with water. Addition of aqueous sodium hydroxide caused first the separation of a dark oil, which was discarded, and then a solid (2·2 g.), m. p. 101°. Repeated crystallisation from carbon tetrachloride afforded 2-amino-6-butoxybenzthiazole as prisms, m. p. 119° (Found: N, 12·7. Calc. for $C_{11}H_{14}ON_2S$: N, 12·6%). F.P. 742,398 cites m. p. 121° for "*p*-butoxyaminobenzthiazole".

x-*Chloro-6-amino-2-butoxybenzthiazole Dihydrochloride.*[*]—2-Chloro-6-nitrobenzthiazole was prepared by the method of Hofmann (*Ber.*, 1880, **13**, 10) from 2-chlorobenzthiazole (Scott and Watt, *J. Org. Chem.*, 1937, **2**, 148). This (10 g.) was dissolved in warm butanol (250 c.c.), a solution of sodium (1·07 g.) in butanol (50 c.c.) added, and the mixture boiled under reflux for 20 hours. After filtration, the solution was evaporated to a small volume, affording 6-*nitro-2-butoxybenzthiazole* (4·15 g.), needles (from chloroform), m. p. 60° (Found: N, 11·2. $C_{11}H_{12}O_3N_2S$ requires N, 11·1%). The foregoing (10 g.) was added to a preheated solution of crystalline stannous chloride (32 g.) in concentrated hydrochloric acid (40 c.c.) at such a rate as to maintain the temperature at 70—80°. The reaction was completed by boiling under reflux for 30 minutes. The solution was then poured into 6N-sodium hydroxide (200 c.c.), and the solution extracted with butanol (4 × 50 c.c.). The combined extracts were dried (K_2CO_3) and hydrogen chloride passed in. The precipitated solid (2·5 g.) was recrystallised from aqueous ethanol, giving x-*chloro-6-amino-2-butoxybenzthiazole dihydrochloride* as needles, m. p. 268° (decomp.) (Found: N, 8·5, 8·7; Cl, 33·4. $C_{11}H_{15}ON_2Cl_3S$ requires N, 8·5; Cl, 32·3%). It dissolved in water to give a solution of low pH which could be adjusted to pH 6 without precipitation.

Di-(*4-phenyl-6-methyl-2-pyrimidyl*) *Disulphide.*—In the preparation of 2-mercapto-4-phenyl-6-methylpyrimidine (Merkatz, *loc. cit.*) a fraction was obtained which was insoluble in ethanol and in dilute hydrochloric acid or sodium hydroxide. It was purified by exhaustive extraction with N-hydrochloric acid. Crystallisation from benzene afforded *di*-(*4-phenyl-6-methyl-2-pyrimidyl*) *disulphide* as yellow rods, m. p. 185·5—186° (Found: N, 13·9; *M*, 397. $C_{22}H_{18}N_4S_2$ requires N, 13·9; *M*, 402). The same compound, m. p. 184—184·5° not depressed by the above, was formed when a solution of the mercaptopyrimidine in dilute sodium hydroxide was oxidised with a slight excess of aqueous iodine solution.

4-*Hydroxy-2-alkylthio-5-methylpyrimidines.*—The appropriate *S*-alkyl*iso*thiourea hydrohalide (1 mol.) was dissolved in one equivalent of 2·5N-sodium hydroxide, and, if necessary, ethanol was added to dissolve precipitated oil or solid. Crude ethyl sodioformylpropionate (1 mol.) was then added with sufficient water to give a clear solution. After 24 hours the solution, filtered if necessary, was acidified with acetic acid, and the product dried and crystallised (see Table III).

4-*Chloro-2-alkylthio-5-methylpyrimidines.*—The 4-hydroxypyrimidine was boiled under reflux with a mixture of phosphorus pentachloride (1 mol.) and an equal weight of phosphorus oxychloride for 45 minutes. Phosphorus oxychloride was distilled off *in vacuo* and the residue poured on crushed ice. The crude solid or oil was isolated with ether and distilled (see Table III).

[*] Experiments by Mr. J. L. Lowe.

4-Amino-2-alkylthio-5-methylpyrimidines.—The chloropyrimidine was heated under pressure at 135—150° with 10% ethanolic ammonia (*ca.* 8—10 parts by weight) for 6—8 hours. The ammonium chloride which separated on cooling was filtered off and the filtrate evaporated. The residue was dissolved in dilute acetic acid, and the product precipitated as a solid by the addition of aqueous sodium hydroxide and crystallised from a suitable solvent (see Table III).

The authors gratefully acknowledge their indebtedness to Mr. C. E. Coulthard, Dr. L. Dickinson, and Miss B. Croshaw for the biological tests. They also thank Miss M. Birchmore and Miss F. Skidmore for carrying out the analyses. The examination of the antituberculous activity of 2-sulphanilamido-5-methyloxadiazole was carried out as part of a collaborative programme of research undertaken by the Therapeutic Research Corporation of Great Britain Ltd.

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

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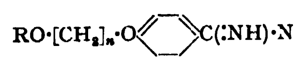
91. *Antituberculous Compounds. Part VI.* p-(*ω-Alkoxyalkoxy*)-N-*arylbenzamidines and Analogues.*

By F. C. COOPER and M. W. PARTRIDGE.

A series of *p*-(*ω*-alkoxyalkoxy)-*N*-arylbenzamidines and certain analogues have been prepared. Comparison of their activities *in vitro* against *Mycobacterium tuberculosis* with those of the diamidines and of the monoamidines described in Parts II and III respectively (*J.*, 1949, 2683, 3043) has extended the earlier observations on the differences in the relation between structure and activity in analogous monoamidines and diamidines and on the significance of the *N*-aryl substituents. Isosteric replacement of methylene by oxygen in the monoamidines apparently causes a marked decrease in activity.

MARKED activity *in vitro* against *Mycobacterium tuberculosis* by di-(*p*-*N*-arylamidinophenoxy)-alkanes (I) and *p*-alkoxy-*N*-arylbenzamidines (II) has been reported in Parts II and III (*J.*, 1949, 2683, 3043) respectively. In these two series, differences were observed in the effects on *in vitro* activity of (*a*) homology in the polymethylene chain of the diamidines and in the alkoxy-group of the monoamidines, (*b*) substitution in the *N*-aryl groups, and (*c*) the presence of serum in the medium during testing. In this communication further experiments on monoamidines are described.

Additional information on the relation between homology and activity was sought through a series of *p*-2-alkoxyethoxy-*N*-phenylbenzamidines (III; $n = 2$, R = alkyl, R′ = Ph). Changes in activity induced by substitution in the *N*-phenyl substituent of the amidine group and by replacement of the *N*-phenyl group by analogous ring systems were also examined in the same series. The preparation of certain analogues of (III) made possible some examination of the significance of the important functional groups in the monoamidine and diamidine series, and of the effect produced by the isosteric replacement of methylene by oxygen.

(I.)


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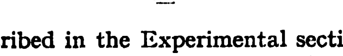
(III.)

The 2-alkoxyethanols described in the Experimental section were obtained in satisfactory yield by the method of Palomaa (*Ber.*, 1902, **35**, 3299); in a number of instances, the corresponding diether of ethylene glycol, as would be expected, was formed as a by-product. We find that 2-dodecyloxyethanol, which is claimed by Halasz (*Bull. Soc. chim.*, 1941, **8**, 170) to have been prepared in very low yield and to have m. p. 51°, has m. p. 22—24°. The values said to have been found and required for the elementary analysis correspond to the composition not of 2-dodecyloxyethanol ($C_{14}H_{30}O_2$) but of a compound, $C_{14}H_{30}O$; recalculation of the published results is not possible because of a misprint in the analytical data; it is unlikely that Halasz's material was 1 : 2-*didodecyloxyethane* ($C_{26}H_{54}O_2$) which we find has m. p. 37—38°. Conversion of the 2-alkoxyethanols into the corresponding chlorides or bromides was readily effected by the procedures of Bennett and Heathcoat (*J.*, 1929, 268) and of Palomaa and Kenetti (*Ber.*, 1931, **64**, 797) respectively. It was difficult to obtain consistent elementary analyses of these alcohols and halides; their purity was therefore checked by determination of the molecular refractions.

The preparative work involved in the production of the substituted phenyl cyanides afforded

	Base.					Picrate.				Activity.*	
	Yield, %.	M. p.	Formula.	Found N, %.	Req., N, %.	M. p.	Formula.	Found N, %.	Req., N, %.	In absence of serum.	In presence of serum.
1. p-(*2-Methoxyethoxy*)-N-*phenylbenzamidine*	85	124—125°	$C_{16}H_{18}O_2N_2$	10·35	10·35	96—98°	$C_{22}H_{21}O_9N_5$	13·9	14·0	5	1
2. p-(*2-Ethoxyethoxy*)-N-*phenylbenzamidine*	73	121—121·5	$C_{17}H_{20}O_2N_2$	9·85	9·85	82—84	$C_{23}H_{23}O_9N_5$	13·3	13·65	10	10
3. p-(*2-Propoxyethoxy*)-N-*phenylbenzamidine*	97	104—104·5	$C_{18}H_{22}O_2N_2$	9·45	9·4	84—86	$C_{24}H_{25}O_9N_5$	13·1	13·3	5—10	10
4. p-(*2-Butoxyethoxy*)-N-*phenylbenzamidine*	99	98—99	$C_{19}H_{24}O_2N_2$	9·1	8·95	79—81	$C_{25}H_{27}O_9N_5$	13·05	12·95	50	10—50
5. p-(*2-Amyloxyethoxy*)-N-*phenylbenzamidine*	85	93—94	$C_{20}H_{26}O_2N_2$	8·65	8·6	83—85	$C_{26}H_{29}O_9N_5$	12·5	12·6	50—100	10
6. p-(*2-Hexyloxyethoxy*)-N-*phenylbenzamidine*	43	97—98	$C_{21}H_{28}O_2N_2$	8·4	8·25	73—76	$C_{27}H_{31}O_9N_5$	12·4	12·3	50	10—50
7. p-(*2-Heptyloxyethoxy*)-N-*phenylbenzamidine*	44	97—98	$C_{22}H_{30}O_2N_2$	8·05	7·9	78—80	$C_{28}H_{33}O_9N_5$	11·8	12·0	—	10
8. p-(*2-Octyloxyethoxy*)-N-*phenylbenzamidine*	49	97—98	$C_{23}H_{32}O_2N_2$	7·9	7·6	76—78	$C_{29}H_{35}O_9N_5$	11·45	11·7	10	10—50
9. p-(*2-Dodecyloxyethoxy*)-N-*phenylbenzamidine*	75	98—99	$C_{27}H_{40}O_2N_2$	6·9	6·6	72—74	$C_{33}H_{43}O_9N_5$	10·75	10·7	—	<1 (10)
10. p-(*2-Hydroxyethoxy*)*benzamidine*	—	—	—	—	—	—	—	—	—	<1	—
11. p-(*2-Hydroxyethoxy*)-N-*phenylbenzamidine*	87	158—160	$C_{15}H_{16}O_2N_2$	10·7	10·95	164—165·5	$C_{21}H_{19}O_9N_5$	14·3	14·45	10—50	5—10
12. p-(*2-Ethoxyethoxy*)*benzamidine*	—	—	—	—	—	—	—	—	—	<1—1	<1—1
13. p-(*3-Ethoxypropoxy*-N-*phenylbenzamidine*	60	85—87	$C_{18}H_{22}O_2N_2$	9·5	9·4	97—99	$C_{24}H_{25}O_9N_5$	13·0	13·3	50	10—50
14. p-(*2-Phenoxyethoxy*)-N-*phenylbenzamidine*	48	203—205	$C_{21}H_{20}O_2N_2$	8·6	8·4	—	—	—	—	<1	—
15. p-(*3-Phenoxypropoxy*)-N-*phenylbenzamidine*	61	128—129	$C_{22}H_{22}O_2N_2$	8·0	8·1	—	—	—	—	500	10
16. p-(*2-Methoxyethoxy*)-N-p′-*propoxyphenylbenzamidine*	95	132—133	$C_{19}H_{24}O_3N_2$	8·8	8·55	97—99	$C_{25}H_{27}O_{10}N_5$	12·7	12·55	—	10
17. p-(*2-Ethoxyethoxy*)-N-p′-*propoxyphenylbenzamidine*	96	122—123	$C_{20}H_{26}O_3N_2$	8·45	8·2	137—139	$C_{26}H_{29}O_{10}N_5$	12·55	12·25	10	10
18. p-(*2-Ethoxyethoxy*)-N-p′-*chlorophenylbenzamidine*	84	115—116	$C_{17}H_{19}O_2N_2Cl$	9·15	8·8	133—134	$C_{23}H_{22}O_9N_5Cl$	13·0	12·8	—	10—50
19. p-(*2-Ethoxyethoxy*)-N-cyclo*hexylbenzamidine*	—	—	—	—	—	—	—	—	—	—	5
20. p-(*2-Ethoxyethoxy*)-N-2′-*pyridylbenzamidine*	—	—	—	—	—	—	—	—	—	—	10
21. p-(*2-Ethoxyethoxy*)-N-*benzylbenzamidine*	—	—	—	—	—	—	—	—	—	10	5—10
22. 3-Ethoxypropanol	—	—	—	—	—	—	—	—	—	—	<1
23. 2-Propoxyethanol	—	—	—	—	—	—	—	—	—	—	<1 (5)
24. 2-Butoxyethanol	—	—	—	—	—	—	—	—	—	—	<1
25. 2-Amyloxyethanol	—	—	—	—	—	—	—	—	—	—	<1
26. 2-*Hexyloxyethanol*	—	—	—	—	—	—	—	—	—	—	1
27. 2-*Heptyloxyethanol*	—	—	—	—	—	—	—	—	—	10	5—10
28. 2-*Octyloxyethanol*	—	—	—	—	—	—	—	—	—	10—50	5—10

* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Figures in parentheses represent dilutions (in thousands) at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

(1), (2) Colourless needles. (3) Colourless plates. (4) Colourless plates. The *picrate* crystallised as yellow plates from aqueous methanol; from aqueous acetic acid, it separated as solvated needles, m. p. 100—102° after sintering at 84° (Found: loss at 55°/vac., 5·05. Found, on dried material, N, 12·7. $C_{25}H_{27}O_9N_5,0·5C_2H_4O_2$ requires $C_2H_4O_2$, 5·25%. $C_{25}H_{27}O_9N_5$ requires N, 12·95%). (5) Colourless plates. (6) Colourless plates. The *benzenesulphonate*, colourless needles from benzene, had m. p. 138—139° (Found: C, 64·75; H, 6·7; N, 5·85. $C_{27}H_{34}O_5N_2S$ requires C, 65·05; H, 6·85; N, 5·6%). (7) Colourless plates. The *picrate* crystallised from aqueous ethanol as thin plates (Found: loss at 55°/vac., 2·8. $C_{28}H_{33}O_9N_5,H_2O$ requires H_2O, 3·0%). (8) Colourless plates. The *benzenesulphonate*, colourless needles from benzene, had m. p. 123—124° (Found: C, 65·8; H, 7·3; N, 5·6. $C_{29}H_{38}O_5N_2S$ requires C, 66·1; H, 7·25; N, 5·3%). (9) Colourless leaflets. The *picrate* crystallised from aqueous ethanol as solvated needles (Found: loss at 20°/vac., 2·6. $C_{33}H_{43}O_9N_5,H_2O$ requires H_2O, 2·7%). (11) Colourless prisms from *iso*propanol. The *amidinium chloride*, colourless prisms from water, had m. p. 143—145° (decomp.) (Found: loss at 100°/vac., 6·4. Found, on dried material, N, 9·45; Cl^-, 11·8; $C_{15}H_{17}O_2N_2Cl,H_2O$ requires H_2O, 5·8%. $C_{15}H_{16}O_2N_2,HCl$ requires N, 9·55; Cl^-, 12·1%). (13), (16) Colourless leaflets. (14) Colourless leaflets from 2-ethoxyethanol. (15) Colourless leaflets from xylene. (17) Colourless plates. The *picrate*, yellow plates from aqueous methanol, melted and effervesced at 110—112°, resolidified, and melted again at 138—139° when not previously dehydrated (Found: loss at 100°/vac., 4·3. $C_{26}H_{29}O_{10}N_5,1·5H_2O$ requires H_2O, 4·5%). (18) Plates (Found: Cl, 10·95. $C_{17}H_{19}O_2N_2Cl$ requires Cl, 11·1%).

little new of chemical interest. For the preparation of the *N*-aryl-substituted amidines described in the table, the arylammonium benzenesulphonate method (Oxley and Short, *J.*, 1946, 147) was used; Pinner's method was applied in the preparation of the unsubstituted amidines, and the aluminium chloride method (Oxley, Partridge and Short, *J.*, 1947, 1110) to that of p-(2-*ethoxyethoxy*)-N-cyclo*hexyl*-, -N-2′-*pyridyl*-, and -N-*benzyl-benzamidine*. The last compound was also obtained, but only in 3% yield, by interaction of benzylammonium thiocyanate and p-(2-*ethoxyethoxy*)*phenyl cyanide* (Partridge and Short, *J.*, 1947, 390). For the determination of activity *in vitro*, the *N*-substituted amidines were obtained in solution as their lactates.

The activities against *M. tuberculosis in vitro* are recorded in the table. The activity of members of the series of p-(2-*alkoxyethoxy*)-N-*phenylbenzamidines* (III; $n = 2$, R′ = Ph, R = Me, Et, Pr^n, Bu^n, n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}, or n-$C_{12}H_{25}$) increases gradually to a maximum when R is C_4—C_6 and then decreases with the higher homologues. In this respect, the series resembles the *p*-alkoxy-*N*-phenylbenzamidines and other series discussed in Part III but differs from the di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II). A large increase in activity in passing from the C_4 to the C_6 homologue, which was observed in the *p*-alkoxy-*N*-phenylbenzamidines, is not apparent here. There is some indication that the presence of serum in the medium during testing inhibits the activity to a lesser extent than in *p*-alkoxy-*N*-phenylbenzamidines, although this inhibiting effect of serum is more pronounced than with the di-(*p*-*N*-arylamidinophenoxy)alkanes. The outstanding feature of the *p*-(2-alkoxyethoxy)-*N*-phenylbenzamidines is their low activity compared with the analogous series described in Part III; this may be ascribed to the replacement of methylene by oxygen. Activities equal to or greater than that shown by 4-aminosalicylic acid, under the same conditions of test, are nevertheless retained.

The dyschemotherapeutic effect of the replacement of methylene by oxygen is best illustrated by a comparison of the isosteres, *p*-hexyloxy-*N*-phenylbenzamidine (Part III) (II; R = n-C_6H_{13}, Ar = Ph) and *p*-(2-propoxyethoxy)-*N*-phenylbenzamidine (III; $n = 2$, R = Pr^n, R′ = Ph) which are active at 1 : 5,000,000 and 1 : 5000—10,000 respectively. A similar but much less marked effect of this type of change in structure is to be observed in the series studied by Friedman *et al.* (*J. Pharm. Exp. Ther.*, 1947, **89**, 153). Some significance may possibly be attached to the position of this second ethereal oxygen atom, since the other isostere which was prepared, namely p-(3-*ethoxypropoxy*)-N-*phenylbenzamidine* (III; $n = 3$, R = Et, R′ = Ph) is active at 1 : 50,000. This feature and the 500-fold increase in activity in passing from p-(2-*phenoxyethoxy*)-N-*phenyl*- (III; $n = 2$, R = R′ = Ph) to p-(3-*phenoxypropoxy*)-N-*phenylbenzamidine* (III; $n = 3$, R = R′ = Ph) are reminiscent of the alternation in activity noted in di-(*p*-*N*-phenylamidinophenoxy)alkanes (I; $n = 2, 3, 4, 5,$ or 6), in which members having an even number of methylene groups were inactive whereas members with an odd number were active.

A comparison of the activities of *p*-(3-ethoxypropoxy)-*N*-phenylbenzamidine, *p*-(3-phenoxypropoxy)-*N*-phenylbenzamidine, and 1 : 3-di-(*p*-*N*-phenylamidinophenoxy)propane (Part II) (I; $n = 3$, Ar = Ph) indicates that in these monoamidines replacement of the 3-ethyl by 3-phenyl enhances activity *in vitro*, but in order to maintain this activity in the presence of serum, a second *N*-phenyl-substituted amidine group is necessary. Replacement of the 2-ethoxy-group of *p*-(2-ethoxyethoxy)-*N*-phenylbenzamidine by hydroxyl (III; $n = 2$, R = H, R′ = Ph) produces no important change in activity, but the ten-fold decrease in activity which occurs in the corresponding unsubstituted *amidines* (III; $n = 2$, R = Et, R′ = H) and (III; $n = 2$, R = R′ = H) provides evidence additional to that noted in Parts II and III of the importance of the *N*-phenyl substituent in the amidine group. The introduction of *p*-propoxy- (III; $n = 2$; R = Me or Et, R′ = p-$PrO{\cdot}C_6H_4$) and *p*-chloro- (III; $n = 2$, R = Et, R′ = p-C_6H_4Cl) groups into the *N*-phenyl groups of *p*-(2-methoxy- and 2-ethoxy-ethoxy)-*N*-phenylbenzamidines produces no important change in activity. As far as comparison is possible, this effect is in accord with what was found in corresponding *p*-alkoxy-*N*-arylbenzamidines reported in Part III and in contrast with the findings for di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II). The *N*-*cyclo*hexyl (III; $n = 2$, R = Et, $R' = -\overline{\mathrm{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2}}$), *N*-2′-pyridyl (III; $n = 2$, R = Et, $R' = -\overline{\mathrm{C{:}N{\cdot}CH{:}CH{\cdot}CH{:}CH}}$), and *N*-benzyl (III; $n = 2$, R = Et, R′ = $-CH_2{\cdot}C_6H_5$) analogues of *p*-(2-ethoxyethoxy)-*N*-phenylbenzamidine are of about the same order of activity as the parent compound.

From the results obtained with seven ω-alkoxyalkanols, it would appear that no special significance may be assigned to the activities of the *heptyl* and *octyl* homologues. Many similar instances of long-chain compounds exhibiting activity against *M. tuberculosis in vitro* have been reported (see, *e.g.*, Walker and Sweeney, *J. Infect. Dis.*, 1920, **26**, 238; Stanley *et al.*, *J. Pharm. Exp. Ther.*, 1932, **45**, 121; Barry, *Nature*, 1946, **158**, 863; D'Arcy Hart, *Brit. Med. J.*, 1946, II, 805; 849; Suter, *Schweiz. med. Woch.*, 1948, **78**, 324; Eiseman, *J. Exptl. Med.*, 1948, **88**, 189). The inhibiting effect of serum observed with the octyl homologue and its acute toxicity (2 mg./g. of body-weight by subcutaneous and by oral administration in mice) render it unlikely that any activity could be demonstrated *in vivo*.

EXPERIMENTAL.

2-*Amyloxyethanol.*—The following method derived from that of Palomaa (*loc. cit.*) was employed. Amyl bromide (151 g.) was gradually added to a solution of sodium (23 g., 1 atom) in hot ethylene glycol (200 g., 3·2 mols.), prepared in an atmosphere of nitrogen. The mixture, after boiling under reflux with stirring for 35 minutes, gave on distillation an azeotrope of ethylene glycol and 2-amyloxyethanol, containing 78% of 2-amyloxyethanol and having b. p. 180—182°/750 mm., d_4^{20} 0·9526, d_4^{25} 0·9499, n_D^{20} 1·4260. After being washed five times with water (50 c.c.), dried ($CaSO_4$), and re-fractionated, this material afforded 2-amyloxyethanol (56 g., 42%), b. p. 187—188°/753 mm., d_4^{20} 0·8926, d_4^{25} 0·8902, n_D^{20} 1·4239, $[R_L]_D$ 37·79 (calc., 37·85). Ashburn *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 1549) record b. p. 188·3°/751·1 mm., d^{25} 0·8893; Tallman (*ibid.*, 1934, **56**, 126) records d_4^{20} 0·8927; n_D^{20} 1·42233; Cretcher and Pittenger (*J. Amer. Chem. Soc.*, 1924, **46**, 1503) record b. p. 181°/745 mm. Low values for the b. p. (cf. also Berry and Michaels, *Quart. J. Pharm.*, 1947, **20**, 331) are probably attributable to an azeotrope of 2-amyloxyethanol with ethylene glycol.

2-*Hexyloxyethanol.*—Hexyl bromide (165 g.) was brought into reaction with a solution of sodium (23 g., 1 atom) in ethylene glycol (200 g., 3·2 mols.) in the same manner as for the foregoing compound, heating being for 2½ hours. The liquid, obtained free from sodium bromide by distillation under reduced pressure, was washed with water and dried ($CaSO_4$); on fractionation 2-*hexyloxyethanol* (78 g., 53%), b. p. 110—112°/27 mm., was obtained (Found: C, 66·2; H, 12·0. $C_8H_{18}O_2$ requires C, 65·7; H, 12·4%), having d_4^{20} 0·8892, n_D^{20} 1·4291, and $[R_L]_D$ 42·40 (calc. 42·46). Berry and Michaels (*loc. cit.*) record, without further details, b. p. 89—93°/17 mm. for this compound. Interaction of ethylene chlorohydrin and sodium hexyloxide in xylene (cf. Cretcher and Pittenger, *loc. cit.*) failed to yield any material of constant b. p.

2-*Heptyloxyethanol*, prepared in 62% yield by the procedure described for the hexyl homologue, had b. p. 124—125°/28 mm. (Found: C, 66·8; H, 12·6. $C_9H_{20}O_2$ requires C, 67·45; H, 12·6%), d_4^{20} 0·8848, n_D^{20} 1·4325, $[R_L]_D$ 47·04 (calc. 47·15). 1 : 2-*Diheptyloxyethane* (9%), obtained from the end-run of the distillation, had b. p. 174—175°/19 mm. (Found: C, 73·8; H, 12·9. $C_{16}H_{34}O_2$ requires C, 74·35; H, 13·25%), d_4^{20} 0·8437, n_D^{20} 1·4330, $[R_L]_D$ 79·60 (calc. 79·92).

2-*Octyloxyethanol.*—Interaction of octyl bromide (193 g.) with ethylene glycol (200 g., 3·2 mols.) containing sodium (23 g., 1 atom) for 4 hours under conditions described for the amyl homologue, followed by distillation, afforded a two-phase distillate. The upper, water-insoluble layer was washed with water, and the washings were used in the recovery of a small quantity of water-insoluble material from the lower layer. The water-insoluble material, after being dried (K_2CO_3), yielded 2-*octyloxyethanol* (90 g., 52%), b. p. 132—133°/22 mm. (Found: C, 68·55; H, 12·4. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·75%), d_4^{20} 0·8811, n_D^{20} 1·4357, $[R_L]_D$ 51·69 (calc. 51·74). This compound is referred to in F.P. 44,641 but no details are given. The end-run from the distillation afforded 1 : 2-*dioctyloxyethane* (7%), b. p. 188—191°/14 mm. (Found: C, 75·6; H, 12·85. $C_{18}H_{38}O_2$ requires C, 75·45; H, 13·35%), d_4^{20} 0·8455, n_D^{20} 1·4369, $[R_L]_D$ 88·76 (calc. 89·09).

2-*Dodecyloxyethanol.*—Prepared in 40% yield by the method described for the foregoing compound, this crystallised as colourless plates, which had m. p. 22—24°, depressed to 14—16° by dodecanol, and b. p. 142°/1·8 mm. (Found: C, 72·4; H, 12·3. Calc. for $C_{14}H_{30}O_2$: C, 73·0; H, 13·15%), d_4^{25} 0·8708, n_D^{25} 1·4432, $[R_L]_D$ 70·17 (calc. 70·33). Henkel et Cie (B.P. 401,142) record b. p. 170—174°/15 mm. The residue in the still contained 1 : 2-*didodecyloxyethane* (25%), colourless plates (from ethanol or *iso*propanol), m. p. 37—38° (Found: C, 78·45; H, 13·55. $C_{26}H_{54}O_2$ requires C, 78·3; H, 13·65%).

Halides.—2-Ethoxyethyl bromide was obtained by interaction of phosphorus tribromide, 2-ethoxyethanol, and pyridine by the method of Palomaa and Kenetti (*loc. cit.*) in 53% yield and had b. p. 126—127°/767 mm. (Vogel, *J.*, 1948, 644, records b. p. 128°/768 mm.). The method of *Org. Synth.*, 1943, **23**, 32, in our hands consistently failed to give better than 38% yield either of this compound or of 2-methoxyethyl bromide.

2-*Propoxyethyl chloride.* Interaction of thionyl chloride (78·5 g.), 2-propoxyethanol (62·5 g., 0·91 mol.), and dimethylaniline (87·2 g., 1·1 mols.) by the method of Bennett and Heathcoat (*loc. cit.*) afforded 2-propoxyethyl chloride (51 g., 69%), b. p. 129—131°/760 mm., n_D^{20} 1·4163 (Karvonen, *Ann. Acad. Sci. Fenn.*, 1912, *A*, **3**, No. 7, 1, gives b. p. 130°/756·3 mm., n_D^{20} 1·41756; Sklyarov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 2121, gives b. p. 119—120°, n_D^{20} 1·426). The method of Foran (*J. Soc. Chem. Ind.*, 1925, **44**, 173T) failed to give any of the desired product when applied to the preparation of 2-propoxyethyl bromide (cf. Bennett and Heathcoat, *loc. cit.*).

2-Butoxyethyl chloride, prepared in 66% yield by the procedure described for the foregoing compound, had b. p. 153—154°/755 mm., n_D^{20} 1·4220. Palomaa and Kenetti (*loc. cit.*) give b. p. 154·5°/750 mm., and Chalmers (*Canad. J. Research*, 1932, **7**, 464) gives b. p. 153—154°, whereas Sklyarov (*loc. cit.*) records b. p. 139—141° and n_D^{20} 1·431.

2-*Amyloxyethyl chloride.* After interaction of thionyl chloride (49 g.), 2-amyloxyethanol (49·6 g., 0·91 mol.), and dimethylaniline (55 g., 1·1 mols.) according to the method of Bennett and Heathcoat (*loc. cit.*), it was found advantageous to remove sulphur dioxide from the ethereal extract of the product by treatment with sodium hydrogen carbonate before drying, evaporation, and fractional distillation; yield, 37·2 g. (66%); b. p. 83—85°/35 mm., 174—175°/763 mm. (Found: C, 55·95; H, 10·3. $C_7H_{15}OCl$ requires C, 55·8; H, 10·05%); d_4^{20} 0·9363; n_D^{20} 1·4261; $[R_L]_D$ 41·22 (calc. 41·15).

2-*Hexyloxyethyl bromide*, prepared in 61% yield by the procedure of Palomaa and Kenetti (*loc. cit.*), had b. p. 121—122°/44 mm. (Found: C, 46·15; H, 7·45; Br, 37·6. $C_8H_{17}OBr$ requires C, 45·95; H, 8·2; Br, 38·2%), d_4^{20} 1·1558, n_D^{20} 1·4504, $[R_L]_D$ 48·66 (calc. 48·65).

2-*Heptyloxyethyl bromide*, prepared in 43% yield in the same way as the foregoing compound, had b. p. 132—133°/38 mm. (Found: C, 48·1; H, 8·4; Br, 35·6. $C_9H_{19}OBr$ requires C, 48·45; H, 8·6; Br, 35·8%), d_4^{20} 1·1298, n_D^{20} 1·4518, $[R_L]_D$ 53·27 (calc. 53·35).

2-*Octyloxyethyl bromide*, prepared in 51% yield in the same way, had b. p. 126—127°/14 mm. (Found: C, 50·0; H, 8·4; Br, 33·6. $C_{10}H_{21}OBr$ requires C, 50·6; H, 8·9; Br, 33·7%), d_4^{20} 1·1085, n_D^{20} 1·4536, $[R_L]_D$ 57·91 (calc. 57·93). The preparation of this compound is claimed in F.P. 44,641 but no confirmatory data are provided.

2-*Dodecyloxyethyl bromide*. A mixture of 2-dodecyloxyethanol (76·8 g.) and pyridine (5 g., 0·2 mol.) was added dropwise to phosphorus tribromide (36·1 g., 0·4 mol.) at 20—40°. After this had been kept overnight, water and ether were added; the ethereal layer was washed with water, dried ($MgSO_4$), and evaporated. Fractional distillation of the residue afforded 2-*dodecyloxyethyl bromide* (56·7 g., 58%), b. p. 132—133°/1 mm. (Found: C, 56·5; H, 9·9; Br, 26·7. $C_{14}H_{29}OBr$ requires C, 57·3; H, 9·95; Br, 27·25%), d_4^{20} 1·0418, n_D^{20} 1·4576, $[R_L]_D$ 76·75 (calc. 76·52).

p-(*ω-Alkoxyalkoxy*)*phenyl Cyanides*.—The cyanides were prepared from sodium *p*-cyanophenoxide and the appropriate *ω*-alkoxyalkyl halide by the method described in Part III (*loc. cit.*). In examples involving the use of an alkoxyalkyl chloride, sodium iodide (0·1 mol.) was added and the period of heating was prolonged to 1—3 days. The following substituted *phenyl cyanides* were prepared: p-(2-*methoxyethoxy*)- (72%), colourless plates, m. p. 43·5—44·5° (Found: N, 8·1. $C_{10}H_{11}O_2N$ requires N, 7·9%); p-(2-*ethoxyethoxy*)- (70%), needles, m. p. 29·5—30·5°, b. p. 112—113°/0·5 mm., 161°/6·5 mm., n_D^{35} 1·5209 (Found: N, 7·4. $C_{11}H_{13}O_2N$ requires N, 7·35%); p-(2-*propoxyethoxy*)- (33%), needles, m. p. 23—24°, b. p. 142—143°/0·6 mm., n_D^{35} 1·5132 (Found: N, 6·85. $C_{12}H_{15}O_2N$ requires N, 6·8%), p-(2-*butoxyethoxy*)- (55%), b. p. 150—151°/0·4 mm., n_D^{35} 1·5080 (Found: N, 6·55. $C_{13}H_{17}O_2N$ requires N, 6·4%); p-(2-*amyloxyethoxy*)- (42%), needles, m. p. 30—31°, b. p. 159—162°/0·6 mm., n_D^{35} 1·5057 (Found: N, 6·1. $C_{14}H_{19}O_2N$ requires N, 6·0%); p-(2-*hexyloxyethoxy*)- (73%), needles, m. p. 33·5—34·5°, b. p. 174—175°/1 mm., n_D^{35} 1·5037 (Found: N, 5·9. $C_{15}H_{21}O_2N$ requires N, 5·65%); p-(2-*heptyloxyethoxy*)- (70%), b. p. 171—174°/0·8 mm., n_D^{35} 1·5012 (Found: N, 5·45. $C_{16}H_{23}O_2N$ requires N, 5·35%); p-(2-*octyloxyethoxy*)- (64%), b. p. 186—190°/2 mm., n_D^{35} 1·4991 (Found: N, 5·15. $C_{17}H_{25}O_2N$ requires N, 5·1%); p-(2-*dodecyloxyethoxy*)- (73%), needles (from ethanol), m. p. 40—42° (Found: N, 4·4. $C_{21}H_{33}O_2N$ requires N, 4·25%); p-(3-*ethoxypropoxy*)- (48%), b. p. 128—129°/0·2 mm., n_D^{35} 1·5155 (Found: N, 7·25. $C_{12}H_{15}O_2N$ requires N, 6·8%).

p-(2-*Hydroxyethoxy*)*phenyl Cyanide*.—Ethylene bromohydrin was boiled under reflux in ethanol for 16 hours with an equivalent of sodium *p*-cyanophenoxide; the solvent was evaporated and the residue was stirred with water and ethyl acetate. Unchanged *p*-cyanophenol was removed from the ethyl acetate solution by N-sodium hydroxide and, after removal of the solvent, the product was crystallised from benzene (yield 61%; m. p. 86·5—87·5°) (Found: N, 8·7. Calc. for $C_9H_9O_2N$: N, 8·6%). Boyd and Marle (*J.*, 1914, **105**, 2138) record m. p. 86°.

p-(2-*Phenoxyethoxy*)*phenyl Cyanide*.—Equimolecular quantities of 2-phenoxyethyl bromide and sodium *p*-cyanophenoxide were boiled together for 16 hours in ethanol; the *product* which separated on addition of water crystallised from light petroleum (b. p. 100—120°) in colourless leaflets (70%), m. p. 112—113° (Found: N, 5·9. $C_{15}H_{13}O_2N$ requires N, 5·9%).

p-(3-*Phenoxypropoxy*)*phenyl cyanide*, obtained in a similar manner to the foregoing compound, crystallised from light petroleum (b. p. 100—120°) as leaflets (79%), m. p. 72—73° (Found: N, 5·6. $C_{16}H_{15}O_2N$ requires N, 5·6%).

p-(*Substituted-alkoxy*)-N-*arylbenzamidines*.—The *p*-(substituted-alkoxy)-*N*-arylbenzamidines described in the table were prepared by heating the appropriate *p*-(substituted-alkoxy)phenyl cyanide with one equivalent of an arylammonium benzenesulphonate at 210° for 1—2 hours (Oxley and Short, *loc. cit.*). The experiments were conducted on a 0·04-g.-mol. scale. A solution of the product in ethanol was treated with aqueous ammonia to liberate the amidine which was purified as the free base, usually after separation from non-basic material as the lactate. Except where otherwise indicated in the footnotes, the amidines were crystallised from light petroleum (b. p. 100—120°). The picrates were prepared by double decomposition of solutions of the amidinium lactates and sodium picrate.

p-(2-*Hydroxyethoxy*)*benzamidine*.—The crude imino-ether hydrochloride, obtained by saturating with dry hydrogen chloride a solution of *p*-(2-hydroxyethoxy)phenyl cyanide (16·3 g.) in dry ethanol (40 c.c.) and keeping 10 days, was shaken for 3 days with saturated ethanolic ammonia (180 c.c.). The *hydrochloride* which separated crystallised as prisms (from dilute hydrochloric acid), m. p. 236—238° (decomp.) (13 g.) (Found: N, 12·7. $C_9H_{13}O_2N_2Cl$ requires N, 12·9%). The *base* (2·9 g.), obtained from the mother-liquors, had m. p. 177—178° (decomp.) (Found: N, 15·3. $C_9H_{12}O_2N_2$ requires N, 15·55%).

p-(2-*Ethoxyethoxy*)*benzamidine*.—A mixture of *p*-(2-ethoxyethoxy)phenyl cyanide (9·6 g.) and dry ethanol (3 c.c.) was treated with dry hydrogen chloride (4·3 g.). The crude imino-ether hydrochloride which separated after 5 days was shaken with saturated ethanolic ammonia (35 c.c.) for 6 days. On being worked up in the usual way, the *amidinium chloride* was obtained as colourless needles which crystallised very slowly from *iso*propanol with solvent of crystallisation and had m. p. 74—76° (4·65 g., 38%) (Found, on material dried at 20°: N, 11·35; Cl^-, 14·35. $C_{11}H_{17}O_2N_2Cl$ requires N, 11·45; Cl, 14·5%). The *picrate* (3·1 g., 14%), obtained from the mother-liquors, crystallised as needles from aqueous ethanol; it melted at 95—96° with effervescence, resolidified, and melted again at 149—151° (Found: loss at 20°/vac., 6·0. Found, on dried material: N, 15·95. $C_{17}H_{19}O_9N_5,1\frac{1}{2}H_2O$ requires H_2O, 5·8%. $C_{17}H_{19}O_9N_5$ requires N, 16·0%). The *benzoate*, plates (from water), had m. p. 204·5—205° (Found: N, 8·4. $C_{18}H_{22}O_4N_2$ requires N, 8·5%).

p-(2-*Ethoxyethoxy*)-N-cyclo*hexylbenzamidine*.—To *p*-(2-ethoxyethoxy)phenyl cyanide (7·65 g.) and *cyclo*hexylamine (4 g., 1 mol.), finely powdered aluminium chloride (5·3 g., 1 mol.) was added portionwise and the mixture was heated at 180° for 10 minutes. Basic material was extracted as the lactate from the precipitate obtained on the addition of sodium hydroxide to an aqueous solution of the melt. p-(2-

Ethoxyethoxy)-N-cyclo*hexylbenzamidine* (4·45 g., 38%), liberated from the lactate, crystallised as colourless plates, m. p. 79—80°, from light petroleum (b. p. 80—100°) (Found : N, 9·85. $C_{17}H_{26}O_2N_2$ requires N, 9·65%). The *picrate* crystallised as short yellow needles from aqueous acetone and had m. p. 60—62° (Found : N, 13·45. $C_{23}H_{29}O_9N_5$ requires N, 13·5%).

p-(2-*Ethoxyethoxy*)-N-2′-*pyridylbenzamidine* was prepared in a similar manner to the foregoing compound from equimolecular quantities of *p*-(2-ethoxyethoxy)phenyl cyanide, 2-aminopyridine, and aluminium chloride in 36% yield; it crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 101—102° (Found : N, 14·95. $C_{16}H_{19}O_2N_3$ requires N, 14·75%). The *monopicrate*, long yellow needles from aqueous ethanol, had m. p. 183—184° (Found : N, 16·35; $C_6H_3O_7N_3$, 44·4. $C_{16}H_{19}O_2N_3,C_6H_3O_7N_3$ requires N, 16·35; $C_6H_3O_7N_3$, 44·5%).

p-(2-*Ethoxyethoxy*)-N-*benzylbenzamidine*.—(i) *p*-(2-Ethoxyethoxy)phenyl cyanide (9·55 g.), benzylamine (5·35 g., 1 mol.), and aluminium chloride (6·7 g., 1 mol.) were brought into reaction in the usual way at 180° for 30 minutes. Basic material, liberated from an aqueous solution of the melt by sodium hydroxide, was collected in chloroform, recovered, purified *via* the lactate, again liberated, collected in chloroform, and recovered. p-(2-*Ethoxyethoxy*)-N-*benzylbenzamidine* slowly crystallised from a solution of the residue in light petroleum (b. p. 100—120°) as plates (3·6 g., 24%), m. p. 80·5—81° (Found : N, 9·5. $C_{18}H_{22}O_2N_2$ requires N, 9·4%). The *picrate*, m. p. 56—58°, was obtained as clusters of yellow needles from aqueous ethanol (Found : loss at 20°/vac., 2·0. Found, on dried material : N, 13·4. $C_{24}H_{25}O_9N_5,\frac{1}{2}H_2O$ requires H_2O, 1·7%. $C_{24}H_{25}O_9N_5$ requires N, 13·3%).

(ii) A mixture of *p*-(2-ethoxyethoxy)phenyl cyanide (9·6 g.) and benzylammonium thiocyanate (8·3 g., 1 mol.), heated at 180° for 105 minutes, afforded, on being worked up in the usual way (Partridge and Short, *loc. cit.*), the amidinium picrate (0·8 g., 3%), m. p. and mixed m. p. 56—58°.

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RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.
UNIVERSITY OF NOTTINGHAM.
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92. *Some* meso-*Amino-acridines and -quinolines derived from 2-Aminodiphenyl.*

By J. H. WILKINSON.

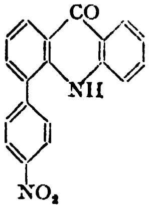
Several new derivatives of 5-aminoacridine and 4-aminoquinoline have been prepared in order to study their effects on mitosis and tissue respiration. Difficulty was experienced in the preparation of 5-*amino*-1-p-*nitrophenylacridine*; the reaction of 1-p-*nitrophenylacridone* with phosphorus oxychloride is discussed.

THE observations of Dustin (*Arch. Exp. Zellforsch.*, 1939, **22**, 395; *Sang*, 1937, **12**, 677) and Bucher (*Z. Zellforsch.*, 1939, **29**, 283) that trypaflavine (acriflavine) possessed a powerful inhibitory effect on mitosis suggested that it might be profitable to study certain other acridine derivatives from this viewpoint. A preliminary report (Lasnitzki and Wilkinson, *Brit. J. Cancer*, 1948, **2**, 369) showed that several other compounds of this type inhibited mitosis in tissue cultures of chick-embryo fibroblasts, and that it would be desirable to extend the study. Recently a number of quaternary salts of heterocyclic compounds has been prepared by Hartwell and Kornberg (*J. Amer. Chem. Soc.*, 1945, **67**, 1606; 1946, **68**, 868, 1131) and some have shown activity against tumour cells (Peters, " Approaches to Tumor Chemotherapy," 1947, p. 244). In the present work therefore, the emphasis was originally placed on the preparation of quaternary salts, but the biological results (Lasnitzki and Wilkinson, *loc. cit.*) have indicated that, with acridine derivatives, quaternisation was not an essential pre-requisite for anti-mitotic activity (contrast O'Connor, *Nature*, 1949, **163**, 408; *Brit. J. Exp. Path.*, 1949, **30**, 30). Several new derivatives of 5-aminoacridine have therefore been prepared with the object of examining their effects on cell division and respiration. Similar 4-aminoquinolines have also been prepared for comparison. The biological results will be published elsewhere.

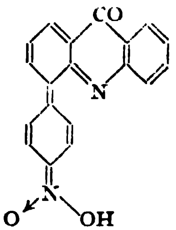
The 5-aminoacridines were prepared by standard methods from the appropriately substituted anilines which were condensed with *o*-chloro- or 2 : 4-dichloro-benzoic acid to give the corresponding diphenylamine-2-carboxylic acids. 4 : 4′-Dinitro-2-aminodiphenyl, however, failed to react under any of the conditions tried, whilst 4′-nitro-2-aminodiphenyl reacted normally to give 2′-p-*nitrophenyldiphenylamine*-2-*carboxylic acid*. The acids were cyclised with phosphorus oxychloride to give the corresponding 5-chloroacridines, but the 1-*p*-nitrophenyl derivative proved so sensitive to hydrolysis that it could be obtained only in minute amounts, the bulk being isolated as 1-p-*nitrophenylacridone*. Interaction with ammonium carbonate in molten phenol by the method of Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169T) gave 5-amino-1-phenylacridine, 8-*chloro*-5-*amino*-1-*phenylacridine*, and 5-*amino*-1-p-*nitrophenylacridine*.

p-Nitrophenylacridone (I) proved highly resistant to phosphorus oxychloride, possibly because of the effect of the nitro-group on the ratio of the contributing resonance forms (cf. Hunter, *J.*, 1945, 806). Thus it is probable that the compound exists largely as the "*ψ*-nitrolic acid" (II), a suggestion supported by the red colour of a solution in alcoholic sodium hydroxide. If this assumption is correct, the proton will not be available for the formation of the 5-hydroxyacridine structure presumably necessary for the promotion of reaction with phosphorus oxychloride. It must be assumed that the effect of the nitro-group is accentuated by transmission through the phenyl group, for 1-nitroacridone, though it does not react under normal conditions with phosphorus oxychloride, undergoes chlorination with phosphorus pentachloride in a high-boiling solvent (Albert and Gledhill, *loc. cit.*; cf. Hampton and Magrath, *J.*, 1949, 1008). *p*-Nitrophenylacridone failed to react with phosphorus pentachloride in xylene.

(I.)



(II.)



Since the principal object in preparing 5-amino-1-*p*-nitrophenylacridine was to reduce it to the corresponding diamino-compound, the very poor yields obtained led to the study of alternative methods. 2′-p-*Aminophenyldiphenylamine*-2-*carboxylic acid* and 1-p-*aminophenylacridone* were obtained by reduction of the respective nitro-compounds with stannous chloride, but neither reacted satisfactorily with phosphorus oxychloride.

The quinoline derivatives were prepared by condensing various 2-aminodiphenyls with ethoxymethylenemalonic ester (Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890; Price and Roberts, *ibid.*, 1946, **68**, 1204; Duffin and Kendall, *J.*, 1948, 893). In most cases the required ethyl 4-hydroxyquinoline-3-carboxylate was obtained, but when 4 : 4′-dinitro-2-aminodiphenyl was used ring closure did not occur and *ethyl* 4′ : 5-*dinitro*-2-*phenylanilinomethylenemalonate* was isolated : several cyclising agents were tried without success. Hydrolysis and decarboxylation gave the 4-hydroxyquinolines which were converted into the 4-chloroquinolines by phosphorus oxychloride. Subsequent treatment with ammonium carbonate in phenol at 180° gave the required 4-aminoquinolines.

An attempt was made to prepare the quaternary 1-methyl derivatives of 4-*amino*-8-*phenyl*- and -8-p-*nitrophenyl-quinoline* by the methods used for the acridine compounds, but this succeeded only in the latter case. The *product* was reduced to the corresponding 4 : 4′-diamino-compound (isolated as its *bromide hydrobromide*).

When 4-*acetamido*-8-*phenylquinoline* was heated with methyl sulphate in nitrobenzene solution and the product hydrolysed with hydrobromic acid, an uncrystallisable oil was obtained. However with methyl toluene-*p*-sulphonate in the absence of a solvent it gave 4-*acetamido*-8-*phenyl*-1-*methylquinolinium toluene*-p-*sulphonate*. Removal of the acetyl group proved difficult, for the compound was recovered unchanged after being heated with 2N-sulphuric acid or hydrobromic acid at 90° for 2 hours. Boiling with 4N-hydrobromic acid, however, not only deacetylated, but also deaminated, the product.

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

5-*Chloro*-2′-*phenyldiphenylamine*-2-*carboxylic Acid*.—A solution of 2 : 4-dichlorobenzoic acid (9·55 g.) in amyl alcohol (40 c.c.) was treated with anhydrous potassium carbonate (7 g.). 2-Aminodiphenyl (8·45 g.) and copper (0·1 g.) were added, and the mixture was refluxed for 6 hours. The amyl alcohol was removed by steam-distillation, and the residue filtered. The ammonium salt of the product was precipitated by the addition of 30% ammonium chloride solution (50 c.c.). This salt was collected and dissolved in 2N-potassium hydroxide, and the free *acid* (8·2 g., 51%) liberated with 2N-hydrochloric acid. It crystallised from toluene in pale yellow prisms, m. p. 203° (Found: C, 70·7; H, 4·5; N, 4·3; Cl, 11·0. $C_{19}H_{14}O_2NCl$ requires C, 70·7; H, 4·3; N, 4·3; Cl, 11·0%).

5 : 8-*Dichloro*-1-*phenylacridine*.—The foregoing acid (2 g.) was refluxed with phosphorus oxychloride (5 c.c.) for 1 hour. Excess of the reagent was removed under reduced pressure, and the residue dissolved in chloroform (30 c.c.). The solution was stirred for 30 minutes with ammonia solution (*d* 0·88; 30 c.c.),

cooled with ice. The chloroform layer was separated and the solvent removed. The *product* (2 g.) crystallised from anhydrous benzene in bright yellow needles, m. p. 164° (Found: N, 4·6; Cl, 21·4. $C_{19}H_{11}NCl_2$ requires N, 4·3; Cl, 21·9%).

8-*Chloro-5-amino*-1-*phenylacridine*.—5 : 8-Dichloro-1-phenylacridine (5 g.) was dissolved in phenol (15 g.) at 80°, and ammonium carbonate (1·5 g.) added. The temperature was raised to 140° for 1 hour. Acetone (70 c.c.) was added to the cooled melt, and the precipitated 8-*chloro-5-amino*-1-*phenylacridine hydrochloride* (3·76 g., 71%) collected. It crystallised from 20% alcohol in bright yellow prisms, m. p. over 300°, sparingly soluble in water (Found: N, 7·25; Cl, 18·3. $C_{19}H_{13}N_2Cl,HCl,3H_2O$ requires N, 7·1; Cl, 18·0%). The *base* was obtained in yellow prisms from chlorobenzene, m. p. 189° (Found: C, 74·4; H, 4·25; N, 8·9. $C_{19}H_{13}N_2Cl$ requires C, 74·8; H, 4·25; N, 9·2%).

The *acetamido*-compound (0·94 g., 82%) was obtained by heating the amino-compound (1 g.) with acetic anhydride (4 c.c.) and acetic acid (2 c.c.) at 105° for 30 minutes, and treating the cooled mixture with benzene (30 c.c.). It crystallised from dioxan in fine pale yellow needles, m. p. 309° (Found: N, 8·35. $C_{21}H_{15}ON_2Cl$ requires N, 8·1%).

8-*Chloro-5-amino*-1-*phenyl*-10-*methylacridinium bromide*. The above acetyl derivative (0·7 g.) was treated with methyl sulphate (0·7 c.c.) in nitrobenzene (7 c.c.) at 140—150° for 1 hour. After treatment with benzene (15 c.c.) overnight, the precipitate was collected and hydrolysed by heating it with 48% hydrobromic acid (5 c.c.) on a water-bath for 1 hour. The *product* (0·6 g., 74%) crystallised from water in bright yellow prisms, m. p. over 300° (Found: N, 7·25. $C_{20}H_{16}N_2ClBr$ requires N, 7·0%).

2′-p-*Nitrophenyldiphenylamine-2-carboxylic Acid*.—*o*-Chlorobenzoic acid (1·56 g.) was dissolved in amyl alcohol (8 c.c.), and the solution treated with potassium carbonate (1·4 g.). 4′-Nitro-2-aminodiphenyl (1·91 g.) and copper (0·1 g.) were added, and the mixture was refluxed for 6 hours. The solvent was removed by steam-distillation and the residue filtered. The filtrate was acidified with acetic acid to precipitate the required *acid* (2·45 g., 81%), which crystallised from 70% alcohol in bright orange-yellow needles, m. p. 243°, sparingly soluble in most organic solvents (Found: C, 68·6; H, 4·3; N, 8·7. $C_{19}H_{14}O_4N_2$ requires C, 68·3; H, 4·2; N, 8·4%).

5-*Amino*-1-p-*nitrophenylacridine*.—2′-*p*-Nitrophenyldiphenylamine-2-carboxylic acid (0·7 g.) was treated with phosphorus oxychloride (2 c.c.) as described for 5 : 8-dichloro-1-phenylacridine. The resultant crude 5-chloro-1-*p*-nitrophenylacridine proved very susceptible to hydrolysis during isolation and it was considered advisable to attempt the conversion of this material into the corresponding 5-amino-compound without further purification. 1-p-*Nitrophenylacridone* (0·45 g.) was obtained as a by-product; this crystallised from pyridine in small pale yellow needles, m. p. 262—263° (Found: N, 8·75. $C_{19}H_{12}O_3N_2$ requires N, 8·9%). The crude 5-chloroacridine (0·25 g.) was dissolved in phenol (1 g.) at 70° and treated with ammonium carbonate (0·1 g.) at 120° for 1 hour. Acetone (10 c.c.) was added to precipitate the yellow hydrochloride, which was sparingly soluble in cold water and underwent rapid hydrolysis to the acridone when an aqueous suspension was heated. The base was obtained by suspending the hydrochloride in 90% alcohol and stirring at 20° with a small excess of 2N-sodium hydroxide. After 1 hour this was collected by filtration and crystallised from chlorobenzene. 5-*Amino*-1-p-*nitrophenylacridine* (90 mg.) was obtained as red needles, m. p. 277—278° (Found: C, 71·5; H, 4·3; N, 13·0. $C_{19}H_{13}O_2N_3$ requires C, 72·3; H, 4·15; N, 13·3%).

1-p-*Aminophenylacridone*.—1-*p*-Nitrophenylacridone (3·16 g.) was finely powdered and heated on a water-bath with stannous chloride (6·8 g.) and hydrochloric acid (50 c.c.) for 2 hours. The mixture was set aside overnight and the solid collected. It was triturated several times with 5N-sodium hydroxide and washed with water. 1-p-*Aminophenylacridone* was thus obtained as a red powder which crystallised from pyridine in irregular orange crystals, m. p. over 300° (Found: N, 9·5. $C_{19}H_{14}ON_2$ requires N, 9·8%).

2′-p-*Aminophenyldiphenylamine-2-carboxylic Acid*.—2′-*p*-Nitrophenyldiphenylamine-2-carboxylic acid (2·75 g.) was heated under reflux with stannous chloride (6 g.) in alcohol (25 c.c.) and hydrochloric acid (*d* 1·16; 15 c.c.) for 3 hours. During this period the solid slowly dissolved. The alcohol was removed by distillation, and the cooled residue treated with saturated sodium acetate solution (100 c.c.). The solid was collected, washed with water, and drained as completely as possible. It was then extracted with three 100 c.c. portions of boiling alcohol. The solvent was removed and the residue dissolved in N/2-sodium hydroxide. Acidification with acetic acid gave 2′-p-*aminophenyldiphenylamine-2-carboxylic acid* which crystallised from 90% alcohol in buff-coloured hexagonal plates, m. p. 188—189° (Found: C, 74·7; H, 5·35; N, 8·9. $C_{19}H_{16}O_2N_2$ requires C, 74·6; H, 5·25; N, 9·2%).

5-2′-*Phenylethylaminoacridine*.—5-Chloroacridine (10·67 g.) was dissolved in phenol (30 g.) at 70°; 2-phenylethylamine (6·1 g.) was added, and the mixture heated at 120° for 1 hour. A green gum was precipitated from the cooled melt by treatment with ether (100 c.c.). When kept, this hardened to a yellow solid which was washed with ether and crystallised twice from methanol. 5-2′-*Phenylethylaminoacridine hydrochloride* (11·7 g., 70%) was thus obtained as lemon-yellow rectangular prisms, m. p. 214—215°, sparingly soluble in water but readily soluble in alcohol (Found: N, 8·1; Cl, 10·9. $C_{21}H_{18}N_2,HCl$ requires N, 8·4; Cl, 10·6%). The *base* was obtained as an oil which crystallised, on treatment with benzene and light petroleum (b. p. 40—60°), in bright yellow irregular crystals, m. p. 79—80°, highly soluble in most organic solvents (Found: C, 84·6; H, 6·25; N, 9·1. $C_{21}H_{18}N_2$ requires C, 84·6; H, 6·0; N, 9·4%). The *acetyl* derivative separated from alcohol in colourless needles, m. p. 230° (Found: N, 8·3. $C_{23}H_{20}ON_2$ requires N, 8·2%).

Quinoline Derivatives.—*Ethyl 4-hydroxy-8-phenylquinoline-3-carboxylate*. 2-Aminodiphenyl (16·9 g.) and ethoxymethylenemalonic ester (21·6 g.) were dissolved in " Dowtherm " (70 c.c.). The temperature of the solution was gradually raised to 270°, and the alcohol eliminated during the reaction collected (10·3 c.c. Theor.: 11·5 c.c.). The *ester* (23·5 g., 80%) which separated from the cooled mixture was collected by filtration and washed successively with benzene and light petroleum (b. p. 40—60°). It crystallised from alcohol in colourless needles, m. p. 249° (Found: C, 73·7; H, 5·5; N, 4·85. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1; N, 4·8%).

4-*Hydroxy-8-phenylquinoline-3-carboxylic acid*. The ethyl ester (20 g.) was heated under reflux with 5N-sodium hydroxide (100 c.c.) for 1½ hours, whereby complete dissolution was obtained. After cooling, the mixture was filtered, diluted with water (200 c.c.), and acidified with hydrochloric acid, to precipitate the *acid* (18 g.), colourless rhombs (from methyl ethyl ketone), m. p. 241—242°, sparingly soluble in alcohol (Found : C, 72·3; H, 4·3; N, 5·15. $C_{16}H_{11}O_3N$ requires C, 72·4; H, 4·2; N, 5·3%).

4-*Hydroxy*-8-*phenylquinoline*. The above acid (16·2 g.) was added during 15 minutes to " Dowtherm " (80 c.c.) maintained at 250° during the addition and for a further 30 minutes. The *base* (13·5 g.) which separated on cooling was collected and washed with light petroleum (b. p. 40—60°); it crystallised from 70% alcohol in colourless plates, m. p. 201° (Found : C, 81·6; H, 5·0; N, 6·5. $C_{15}H_{11}ON$ requires C, 81·4; H, 5·0; N, 6·35%).

4-*Chloro*-8-*phenylquinoline*. 4-Hydroxy-8-phenylquinoline (2·2 g.) was heated under reflux for 2 hours with phosphorus oxychloride (6 c.c.). The cooled solution was poured on crushed ice (30 g.) and made alkaline with aqueous ammonia. The gum which separated hardened to a white solid (2·27 g., 95%) on trituration with dilute aqueous ammonia. It was collected by filtration and dried over calcium chloride. 4-*Chloro*-8-*phenylquinoline* crystallised from alcohol in colourless needles, m. p. 93° (Found : C, 75·1; H, 4·1; N, 5·65; Cl, 15·0. $C_{15}H_{10}NCl$ requires C, 75·1; H, 4·2; N, 5·85; Cl, 14·85%).

4-*Amino*-8-*phenylquinoline*. 4-Chloro-8-phenylquinoline (2 g.) was dissolved in phenol (6 g.) at 70° and treated with powdered ammonium carbonate (1 g.). The temperature was raised to 180° for 2 hours. After cooling, the hydrochloride of the product was precipitated with acetone (50 c.c.) and converted into the *base* (1·1 g.) with aqueous sodium hydroxide. It crystallised from toluene in colourless prisms, m. p. 166° (Found : C, 81·8; H, 5·45; N, 12·8. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·45; N, 12·7%). The *acetyl* derivative separated from alcohol in colourless cubes, m. p. 206—207° (Found : C, 77·8; H, 5·45; N, 10·9. $C_{17}H_{14}ON_2$ requires C, 77·9; H, 5·35; N, 10·7%).

4-*Acetamido*-8-*phenyl*-1-*methylquinolinium toluene*-p-*sulphonate*. A mixture of 4-acetamido-8-phenylquinoline (1 g.) and methyl toluene-*p*-sulphonate (1 g.) was heated at 160° for 30 minutes. The cooled melt was crushed and triturated with hot benzene. The residual *salt* crystallised from water or alcohol in colourless needles, m. p. 254–255° (Found : C, 67·1; H, 5·4; N, 6·3; S, 7·1. $C_{25}H_{24}O_4N_2S$ requires C, 67·0; H, 5·36; N, 6·3; S, 7·1%).

Attempted Hydrolysis of 4-*Acetamido*-8-*phenyl*-1-*methylquinolinium toluene*-p-*sulphonate*. (i) The quaternary salt (0·32 g.) was heated on a steam-bath with 2N-sulphuric acid (3 c.c.) for 1 hour. The solid (0·21 g.) which separated on cooling had m. p. 254° and proved to be unchanged starting material (Found : N, 6·5; S, 7·4%). (ii) Similar treatment with 2N-hydrobromic acid also failed to hydrolyse the toluene-*p*-sulphonate. (iii) 0·5 G. of the salt was heated under reflux with 4N-hydrobromic acid (5 c.c.) for 2 hours. The oil which separated on cooling soon hardened to a solid, which was dissolved in hot water. The resulting solution was made alkaline with sodium hydroxide, and the precipitate produced was dissolved in hot 2N-hydrobromic acid. After two recrystallisations from water, the solid which separated on cooling, was obtained in colourless prisms, m. p. 155—156°. It contained no bromine, was devoid of basic properties, and evidently consisted of 4-*hydroxy*-2-*keto*-8-*phenyl*-1-*methyl*-1 : 2-*dihydroquinoline* or its tautomer (Found : C, 76·1; H, 6·1; N, 5·0. $C_{16}H_{14}O_2N$ requires C, 76·3; H, 5·55; N, 5·55%).

Ethyl 4-*hydroxy*-8-p-*nitrophenylquinoline*-3-*carboxylate*. 4′-Nitro-2-aminodiphenyl (10·7 g.) and ethoxymethylenemalonic ester (10·8 g.) were heated in " Dowtherm " (40 c.c.) as described above. The theoretical amount of alcohol was eliminated after 2 hours. The product (13·9 g., 82%), which crystallised, was washed with benzene and light petroleum (b. p. 40—60°). The *ester* was sparingly soluble in most organic solvents, and separated from aqueous pyridine in pale yellow masses, m. p. 285° (Found : C, 63·7; H, 4·2; N, 8·5. $C_{18}H_{14}O_5N_2$ requires C, 63·9; H, 4·15; N, 8·3%).

4-*Hydroxy*-8-p-*nitrophenylquinoline*. The ester (13 g.) was hydrolysed by being heated under reflux with 2N-sodium hydroxide (200 c.c.) for 1 hour. The resulting solution was filtered while still hot, and the quinoline-3-carboxylic acid (12 g.) precipitated with hydrochloric acid. It was obtained as a pale yellow powder, m. p. 280° (decomp.), very sparingly soluble in organic solvents. No suitable solvent for crystallisation was found. The acid (12 g.) was gradually added to boiling " Dowtherm " (60 c.c.), and the mixture maintained at 250—260° for 1 hour and then cooled. The product (9·85 g., 95%) was collected, washed with benzene and light petroleum (b. p. 40—60°), and dried at 100°. It crystallised from 70% aqueous pyridine in yellow irregular prisms, m. p. >300°, sparingly soluble in most organic solvents (Found : N, 10·7. $C_{15}H_{10}O_3N_2$ requires N, 10·4%).

4-*Chloro*-8-p-*nitrophenylquinoline*. 4-Hydroxy-8-*p*-nitrophenylquinoline (9·5 g.) was refluxed with phosphorus oxychloride (20 c.c.) for 2 hours. The mixture was cooled, poured on crushed ice, and neutralised with aqueous ammonia. The solid *base* (10·15 g., 100%) crystallised from 80% aqueous dioxan in fine pale yellow needles, m. p. 224° (Found : N, 9·6. $C_{15}H_9O_2N_2Cl$ requires N, 9·75%).

4-*Amino*-8-p-*nitrophenylquinoline*. 4-Chloro-8-*p*-nitrophenylquinoline (9·7 g.) was dissolved in phenol (27 g.) at 100°, and ammonium carbonate (4 g.) was added portionwise whilst the temperature was raised to 180° for 2 hours. The product (5·8 g., 65%) was isolated in the same manner as 4-amino-8-phenylquinoline. 4-*Amino*-8-p-*nitrophenylquinoline* crystallised from alcohol in lemon-yellow, squat prisms, m. p. 224—225° (Found : C, 67·6; H, 4·15; N, 16·0. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·15; N, 15·8%). The *acetyl* derivative crystallised from alcohol in pale yellow needles, m. p. 242° (Found : N, 13·8. $C_{17}H_{13}O_3N_3$ requires N, 13·65%).

4-*Amino*-8-p-*nitrophenyl*-1-*methylquinolinium bromide*. 4-Acetamido-8-*p*-nitrophenylquinoline (1·9 g.) was dissolved in nitrobenzene (7 c.c.) and treated with methyl sulphate (2 c.c.) at 150° for 1 hour. The cooled mixture was treated with benzene (25 c.c.) and set aside for 4 hours. The gum was washed by decantation with benzene and hydrolysed with 48% hydrobromic acid (10 c.c.) on a steam-bath for 1 hour. The product (1·9 g., 85%) was collected and washed with water. 4-*Amino*-8-p-*nitrophenyl*-1-*methylquinolinium bromide* crystallised from water in pale yellow plates, m. p. 279—281° (decomp.) (Found : N, 11·6. $C_{16}H_{14}O_2N_3Br$ requires N, 11·7%). An aqueous solution gave no precipitate with saturated sodium hydrogen carbonate solution, but sodium hydroxide precipitated the yellow ψ-base.

4 : 4′-*Diamino*-8-*phenyl*-1-*methylquinolinium bromide hydrobromide*. The nitro-salt (1·5 g.) was suspended in 4N-hydrochloric acid (8 c.c.) and treated with stannous chloride (3 g.) under reflux for 3 hours. The cooled mixture was diluted with water (30 c.c.) and made alkaline to phenolphthalein with

5N-sodium hydroxide. The solid base was collected and washed with water. It was dissolved in hot 2N-hydrobromic acid (20 c.c.) and, on cooling, the required *bromide hydrobromide* (1·29 g., 94%) separated. It crystallised from water in buff-coloured needles, m. p. >300°, charring at *ca.* 295° (Found: N, 9·0; Br, 34·8. $C_{16}H_{16}N_3Br,HBr,3H_2O$ requires N, 9·0; Br, 34·4%).

Attempted Preparation of 4′ : 5-Dinitro-4-hydroxy-8-phenylquinoline.—4 : 4′-Dinitro-2-aminodiphenyl (12·95 g.) and ethoxymethylenemalonic ester (10·8 g.) were heated with " Dowtherm " (50 c.c.) at 250° for 4 hours, after which no more alcohol distilled off. Only half of the theoretical amount was obtained. On cooling, *ethyl 4′ : 5-dinitro-2-phenylanilinomethylenemalonate* (12·1 g., 56%) separated. This crystallised from alcohol in bright yellow needles, m. p. 188°, sparingly soluble in most organic solvents, but readily soluble in dioxan and *p*-tolyl methyl ether (Found: C, 55·8; H, 4·55; N, 9·8. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·45; N, 9·75%). Several methods of cyclisation including heating with sulphuric and phosphoric acids were attempted, but in no case was the required ethyl 4′ : 5-dinitro-8-phenyl-4-quinolone-3-carboxylate obtained.

The writer expresses his thanks to Messrs. May and Baker Ltd. for gifts of chemicals, to Professor N. F. Maclagan for his interest, and to Miss Edna Peat for experimental assistance. The cost of the microanalyses was defrayed by a grant to Westminster Hospital from the British Empire Cancer Campaign.

Department of Chemical Pathology,
Westminster Medical School (University of London),
17, Horseferry Road, London, S.W.1.

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93. *The Structure of Molecular Compounds. Part IX. A Compound of Xenon and Quinol.*

By H. M. Powell.

The preparation of the compound of composition $3C_6H_4(OH)_2,0{\cdot}88Xe$ is described. The compound, similar in properties and structure to the corresponding argon and krypton compounds, contains 26% of xenon.

In Parts VII and VIII (*J.*, 1950, 298, 300) the preparation of compounds of quinol with argon and with krypton was described, and from consideration of the sizes of inert-gas atoms, which in these compounds are enclosed in a cage structure formed by hydrogen-bonded quinol molecules, it seemed probable that xenon would also fit into the cavity and thus form a similar compound.

The preparation was carried out in the manner previously described (Part VII) by cooling an aqueous solution of quinol in a pressure-vessel containing xenon. With the material available the highest pressure obtainable was 14 atmospheres. In these conditions the product obtained in the first experiment contained xenon but did not, as in the case of the argon and krypton compounds, contain large crystals suitable for separation by sieving or hand picking from any α-quinol present. From the loss of weight on heating it was found to have about one-third of the xenon content expected for the formula $3C_6H_4(OH)_2,Xe$. The product was not homogeneous and contained a small proportion of material of density greater than that of carbon tetrachloride but the bulk of it had a lower density. A second preparation gave 2 g. of product from which a few stumpy crystals of about 1 mm. diameter were separated by hand. Most of the product was then thrown into carbon tetrachloride and the main portion removed by flotation. About 0·1 g. of a dense fraction that sank in carbon tetrachloride was separated, and the xenon content determined. This part contained 26% of xenon [$3C_6H_4(OH)_2,Xe$ requires Xe, 28·5%]. The composition of the analysed sample may be represented as $3C_6H_4(OH)_2,0{\cdot}88Xe$, *i.e.*, 88% of the available cavities contain a xenon atom. The density of the hand-picked crystals was determined by flotation in mixtures of carbon tetrachloride and ethylene dibromide. The highest value observed was 1·69 g./c.c. The density calculated for the xenon compound, on the assumptions that it has the same unit cell dimensions as the argon compound and that all the cavities are occupied, is 1·77 g./c.c. The observed value corresponds to a composition $3C_6H_4(OH)_2,0{\cdot}84Xe$. The high density readily distinguishes the substance from the quinol compounds of argon or krypton, which have calculated maximum values of 1·42 and 1·59 g./c.c., respectively, and as prepared have somewhat lower values than those calculated.

The crystals are colourless and show no signs of decomposition after several days. On dissolution they liberate xenon, and, on heating, quinol volatilises and thus sets free xenon. A preliminary *X*-ray examination shows that they have a unit cell similar to those of the argon and krypton compounds.

The less dense fraction of the yield removed by flotation with carbon tetrachloride contained 10% of xenon. It may be a mixture but has not been examined in detail.

The author expresses his thanks to the British Oxygen Co., who prepared a suitable cylinder of xenon for this work.

Laboratory of Chemical Crystallography,
University Museum, Oxford.

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94. o-*Mercapto-azo-compounds. Part I. The Coupling of Tetrazotised 2 : 2'-Diaminodiphenyl Disulphide with β-Naphthol.*

By A. Burawoy and C. Turner.

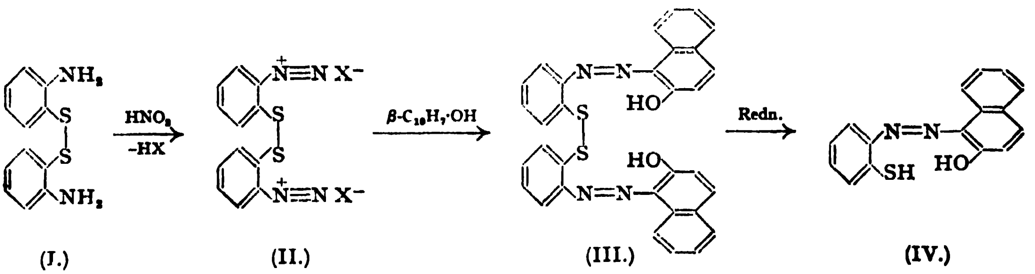
A general method for the preparation of the hitherto unknown *o*-mercapto-azo-compounds is developed.

Only monodiazotisation of 2 : 2'-diaminodiphenyl disulphide occurs in dilute acid, the product decomposing spontaneously to yield benz-1-thia-2 : 3-diazole (V). The tetrazonium salt (II) is formed and is stable in concentrated sulphuric acid, but is also decomposed by water with the formation of benzthiadiazole.

Coupling takes place when the concentrated sulphuric acid solution is added directly to solutions or suspensions of β-naphthol in aqueous sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium acetate, or pyridine. Three different reactions are encountered. In all cases an intermediate product (XXX), formed by coupling with one mole of β-naphthol, is first formed. In sodium hydroxide and carbonate solution this decomposes to benzthiadiazole and unstable *o*-(2-hydroxynaphthalene-1-azo)benzenesulphenic acid (XXXI), which undergoes spontaneous disproportionation in sodium hydroxide solution, to yield di-*o*-(2-hydroxynaphthalene-1-azo)phenyl disulphide (III) and *o*-(2-hydroxynaphthalene-1-azo)benzenesulphinic acid (IX), whereas in sodium carbonate solution condensation with a second mole of β-naphthol to *o*-(2-hydroxynaphthalene-1-azo)phenyl 2-hydroxy-1-naphthyl sulphide (X) takes place. On the other hand, the intermediate (XXX) is sufficiently stable in sodium hydrogen carbonate or acetate solution or in pyridine to allow coupling with a second mole of β-naphthol in preference to degradation, the disulphide (III) being formed in good yield.

The mechanisms of these reactions are confirmed by independent experiments, and the structures of the products are established by unambiguous methods.

Owing to their technical and theoretical importance, *o*-hydroxy-azo-compounds have been the subject of numerous investigations. A study of the properties of the corresponding *o*-mercapto-azo-compounds should also be of interest. Such substances are as yet unknown, partly because the methods normally used in the preparation of the *o*-hydroxy-azo-compounds (reaction of a diazo-compound with a phenol coupling in the *o*-position, and reaction of a diazotised *o*-aminophenol with a suitable coupling component) are not applicable in this series. Thus, thiophenols are unable to couple, forming instead the corresponding diazothio-ethers Ar·N:N·SAr' which apparently cannot be rearranged to yield azo-compounds (Ziegler, *Ber.*, 1890, **23**, 2471; Stadler, *Ber.*, 1884, **17**, 2076; Hantzsch and Freese, *Ber.*, 1895, **28**, 3237; Dunn and Fletcher, *Trans Kansas Acad. Sci.*, 1934, **37**, 123), and *o*-aminothiophenols yield on diazotisation the non-coupling benz-1-thia-2 : 3-diazoles (cf. Bernthsen, *Annalen*, 1889, **251**, 30; Jacobson *et al.*, *ibid.*, 1893, **277**, 209, 237, 257).

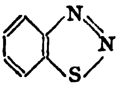


(I.) (II.) (III.) (IV.)

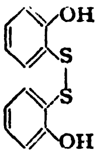
A few *o*-alkylthio-azo-compounds have been prepared, but only 2 : 2'-di(methylthio)azobenzene (Brand, *Ber.*, 1909, **42**, 3463) and 5-nitro-2-methylthiobenzeneazo-β-naphthol (Hodgson and Dodgson, *J.*, 1948, 870) appear to have been obtained in a pure state.

We first considered the possibility of tetrazotising 2 : 2'-diaminodiphenyl disulphide (I), coupling the tetrazonium salt (II) with β-naphthol, and finally reducing the di-*o*-(2-hydroxynaphthalene-1-azo)phenyl disulphide (III) formed to 1-(*o*-mercaptobenzeneazo)-2-naphthol (IV). Although we have succeeded in our aim, the reactions proved to be very complex.*

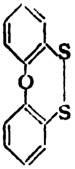
Previous attempts to prepare the tetrazonium salt of 2 : 2′-diaminodiphenyl disulphide or to couple it have been unsuccessful. Jacobson (*Ber.*, 1887, **20**, 1902) mentioned that boiling diazotised 2 : 2′-diaminodiphenyl disulphide with water yields the steam-volatile benz-1-thia-2 : 3-diazole (V). Hodgson (*J. Soc. Dyers and Col.*, 1924, **40**, 330) obtained a 50% yield of (V) on diazotising the diamine in dilute mineral acids, no coupling with β-naphthol being observed. Guha and Ghosh (*J. Indian Inst. Sci.*, 1929, **12**, *A*, 31) claimed the isolation of the tetrazonium salt (II), describing it as insoluble in water and unable to react with aniline or potassium ethyl xanthate; they also stated that it decomposed when stored at > 20° or on subjection to the action of reducing agents or of coupling components, with the formation of a brown tar which, on steam-distillation, yielded (VII) by dehydration of di-*o*-hydroxyphenyl disulphide (VI). Not only does this contrast with Jacobson's and Hodgson's earlier observations, but (VI) has already been described by Haitinger (*Monatsh.*, 1883, **4**, 165) as stable up to 200°.



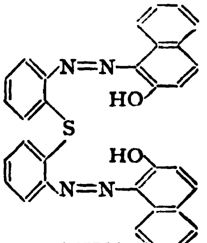
(V.)



(VI.)



(VII.)



(VIII.)

Re-investigating the action of nitrous acid on 2 : 2′-diaminodiphenyl disulphide, we found, in agreement with Hodgson, that in dilute hydrochloric or sulphuric acid benzthiadiazole contaminated with varying amounts of resinous material separates immediately on addition of sodium nitrite, and that it can be isolated in 45—60% yield by ether-extraction. We do not confirm Guha and Ghosh's claims. The supposed tetrazonium salt decomposing above 20° is undoubtedly impure benzthiadiazole which melts at about 24° and solidifies again on cooling. Steam-distillation yields pure benzthiadiazole, but no (VII).

The tetrazonium *salt* (II) is formed when diazotisation is carried out in concentrated sulphuric acid with nitrosylsulphuric acid. It is stable in this medium, but is slowly decomposed by water with the formation of benzthiadiazole. When the sulphuric acid solution is poured into ice-water and the resultant clear solution immediately extracted with ether, only traces of benzthiadiazole are obtained. However, it soon begins to separate and after about three hours can be extracted in about 75% yield. This, incidentally, compares favourably with other known methods of preparation.

The slow degradation of the tetrazonium salt (II) in water is also indicated by coupling samples of the solution with β-naphthol in aqueous sodium hydroxide. The amount of the violet-red disulphide (III) formed (cf. below) slowly decreases with time when the tetrazonium solution is set aside (at 0°) before coupling, and after a few hours' storage none is obtained. In its place a small amount (< 5%) of an orange-brown azo-compound is formed which has been identified as *di*-o-(*2-hydroxynaphthalene*-1-*azo*)*phenyl sulphide* (VIII) by unambiguous synthesis from tetrazotised 2 : 2′-diaminodiphenyl sulphide and β-naphthol.

Treatment of the sulphuric acid solution of the tetrazonium salt with aqueous cuprous chloride gives, not 2 : 2′-dichlorodiphenyl disulphide, but an orange-brown *complex* of benzthiadiazole and cuprous chloride, the yield of benzthiadiazole obtained by ether-extraction after addition of sodium hydroxide being about 84%.

Since the tetrazonium salt is decomposed by the action of water, coupling was carried out by direct addition of the concentrated sulphuric acid solution to alkaline solutions (or suspensions) of β-naphthol. The resultant products varied considerably with the nature of the alkali used. Three distinct reactions may occur which, fortunately, can be realised separately by coupling in aqueous solutions of (i) sodium hydroxide, (ii) sodium carbonate, and (iii) sodium hydrogen carbonate, sodium acetate, or pyridine.

In the first case, benzthiadiazole (V), the *disulphide* (III) (which dissolves in organic solvents with a characteristic violet colour), and bright red sodium *o*-(2-hydroxynaphthalene-1-azo)-benzenesulphinate (as IX) are formed.

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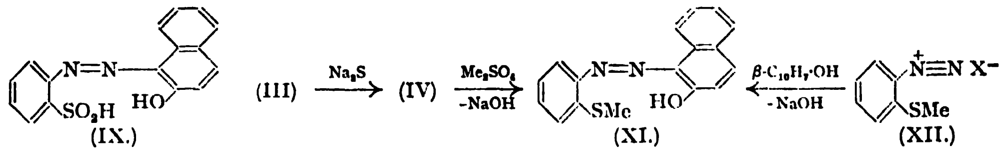
* *o*-Hydroxyazo-compounds are formulated in this paper for convenience as azo-compounds, although they may actually be phenylhydrazones (cf. Burawoy and Markowitsch, *Annalen*, 1933, **503**, 180).

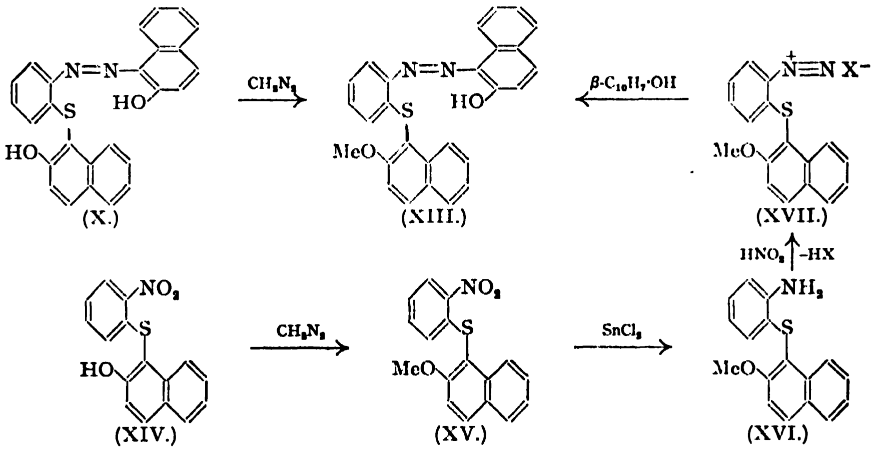
Coupling with the sodium salt of β-naphthol in excess of sodium carbonate yields benzthiadiazole and the reddish-brown o-(2-*hydroxynaphthalene*-1-*azo*)*phenyl* 2-*hydroxy*-1-*naphthyl sulphide* (X). No disulphide (III) or sulphinic acid (IX) can be isolated.

Finally, in excess of sodium hydrogen carbonate, sodium acetate, or pyridine, the disulphide (III) is obtained alone and in good yield.

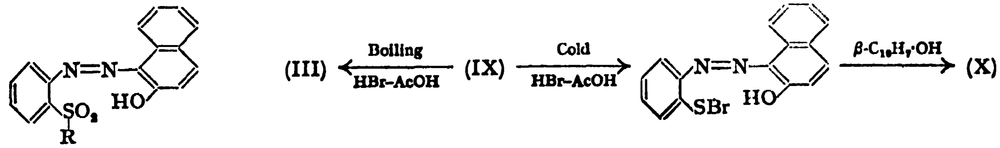
The structures of the various azo-compounds isolated were determined as follows. The disulphide (III) was reduced with sodium sulphide at room temperature and subsequently methylated with methyl sulphate to give 1-(o-*methylthiobenzeneazo*)-2-*naphthol* (XI), identical with a product synthesised unambiguously by coupling diazotised *o*-methylthioaniline (XII) with β-naphthol.



Acidification of an aqueous or alcoholic suspension of the sparingly soluble bluish-violet sodium salt of 1-(*o*-mercaptobenzeneazo)-2-naphthol with hydrochloric or acetic acid at room temperature yields the orange-red thiol itself, the first *o*-mercapto-azo-compound to be isolated. It is very sensitive to heat. In solution or in the solid state it is easily converted into a brown alkali-insoluble product. Its structure and the properties of *o*-mercapto-azo-compounds will be discussed elsewhere.



The sulphide (X) yields with diazomethane the 2′-*methyl ether* (XIII), the hydroxyl group in 1-benzeneazo-2-naphthol being unreactive under these conditions (cf. Kuhn and Bär, *Annalen*, 1935, **516**, 143). The structure of this ether was established by unambiguous synthesis from *o*-nitrophenyl 2-hydroxy-1-naphthyl sulphide (XIV) (Zincke and Farr, *ibid.*, 1912, **391**, 55) by methylation with diazomethane to (XV), reduction with stannous chloride to the *amine* (XVI), diazotisation to give (XVII), and finally coupling with β-naphthol.



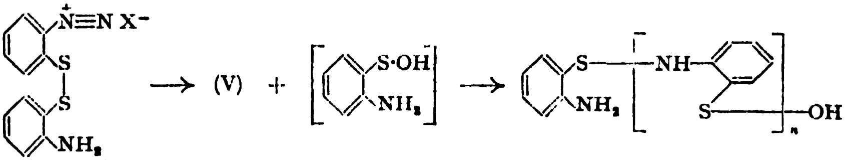
(XVIII; R = Me)
(XIX; R = *p*-NO_2·C_6H_4·CH_2)

The sulphinic acid (IX) obtained from its water-soluble sodium salt by the addition of hydrochloric acid was characterised as o-(2-*hydroxynaphthalene*-1-*azo*)*phenyl methyl sulphone* (XVIII) and the corresponding p-*nitrobenzyl sulphone* (XIX). Its structure, besides being suggested by general properties characteristic of sulphinic acids, was established by conversion (i) by hydrogen bromide in boiling glacial acetic acid into the disulphide (III), and (ii) by hydrogen bromide in cold glacial acetic acid into o-(2-*hydroxynaphthalene*-1-*azo*)*benzenesulphenyl bromide* (XX), and condensation of the latter with β-naphthol in quantitative yield to the sulphide (X).

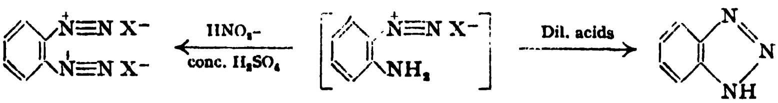
Aromatic sulphinic acids $ArSO_2H$ are known to yield, with hydrogen bromide in glacial acetic acid, either the corresponding sulphenyl bromides ArSBr or the disulphides ArS·SAr depending on the reaction temperature and the nature of the sulphinic acid (Fries and Schürmann, *Ber.*, 1914, **47**, 1195); and aromatic sulphenyl halides are known to react with β-naphthol in suitable conditions to form 1-arylthio-2-naphthols (Zincke and Farr, *loc. cit.*; Fries, *Ber.*, 1912, **45**, 2965).

DISCUSSION.

The spontaneous separation of benzthiadiazole on addition of sodium nitrite in dilute hydrochloric and sulphuric acids shows that the diazotisation of 2 : 2′-diaminodiphenyl disulphide proceeds, in the main, only as far as the monodiazonium salt (XXI). This spontaneously splits into benzthiadiazole (V) and probably aniline-2-sulphenic acid (XXII) which may undergo condensation to (XXIII) or other more complicated changes, yielding some unidentified resinous products. Any tetrazonium salt formed would decompose only slowly, with the formation of benzthiadiazole (cf. above). This is similar to the behaviour of *o*-phenylenediamine which cannot be tetrazotised in dilute acids, the monodiazonium salt (XXIV) spontaneously condensing internally with the formation of benztriazole (XXV) (Ladenburg, *Ber.*, 1876, **9**, 219), whereas in concentrated sulphuric acid the reaction proceeds to the stable tetrazonium salt (XXVI) (Hodgson and Walker, *J.*, 1935, 530).

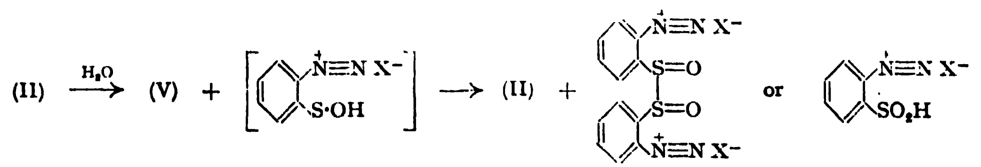


(XXI.) (XXII.) (XXIII.)



(XXVI.) (XXIV.) (XXV.)

The slow decomposition of the tetrazonium salt (II) on addition of its solution in concentrated sulphuric acid to ice-water should yield benzthiadiazole (V) and diazobenzene-2-sulphenic acid (XXVII) (or its anhydride) in equimolecular proportions. Since at least 70% of benzthiadiazole is recovered, the sulphenic acid must have undergone further changes which have not yet been fully elucidated.



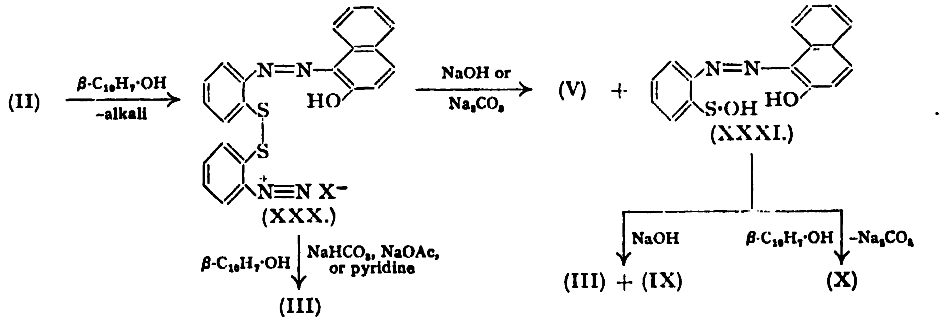
(XXVII.) (XXVIII.) (XXIX.)

Substances forming the unstable sulphenic acids ArS·OH (such as the sulphenyl halides ArSX) are known to undergo easy disproportionation to the corresponding disulphides ArS·SAr and either disulphoxides ArSO–SOAr or sulphinic acids $ArSO_2H$ (Zincke and Farr, *loc. cit.*). Therefore it would be reasonable to assume that diazobenzene-*o*-sulphenic acid (XXVII) would behave similarly and would form the tetrazonium salt (II) which would again decompose yielding an additional amount of benzthiadiazole, and either the tetrazonium salt of 2 : 2′-diaminodiphenyl disulphoxide (XXVIII) or diazobenzene-*o*-sulphinic acid (XXIX). However, coupling with alkaline β-naphthol yields, rather surprisingly, instead of the corresponding azo-compounds, the monosulphide (VIII). Our experiments do not afford any evidence for the mechanism of the formation of tetrazotised 2 : 2′-diaminodiphenyl sulphide, but we have ascertained that it is not due to the presence of a small amount of 2 : 2′-diaminodiphenyl sulphide in the starting material.

The almost spontaneous formation of benzthiadiazole by the action of cuprous chloride on the tetrazonium salt (II) indicates either (i) its direct reduction, or (ii) its degradation to benzthiadiazole and diazobenzene-*o*-sulphenic acid (cf. above) followed by reduction of the latter. Since the degradation in absence of cuprous chloride is only slow, the former interpretation is more likely.

The reaction of the tetrazonium salt (II) with β-naphthol in sodium hydroxide solution is initiated by coupling with one mole of β-naphthol which is followed by degradation of the intermediate (XXX) to benzthiadiazole (V) and the salt of *o*-(2-hydroxynaphthalene-1-azo)-benzenesulphenic acid (XXXI). The latter, like all known substances forming sulphenic acids as intermediate with sodium hydroxide (such as the sulphenyl halides), will quickly undergo disproportionation to equimolecular quantities of the disulphide (III) and the sodium sulphinate (IX). This interpretation is supported (i) by the yields of disulphide and sulphinic acid obtained, which would correspond to about 90% of theory, and (ii) by the analogous disproportionation of the sulphenyl bromide (XX) with sodium hydroxide at room temperature, which is also initiated by the formation of the sodium sulphenate (XXXI).

For various reasons, it is unlikely that the degradation of the tetrazonium salt (II) to benzthiadiazole and sodium diazobenzene-*o*-sulphenate takes place first and is followed by the coupling of this diazo-compound with β-naphthol and, finally, disproportionation. Thus, the disulphide (III) is not formed if the tetrazonium solution in concentrated sulphuric acid is first added to sodium hydroxide, sodium carbonate, or sodium hydrogen carbonate alone and then quickly treated with β-naphthol. The separation of benzthiadiazole, *i.e.*, degradation, is spontaneous in these conditions.



Coupling of tetrazotised 2 : 2′-*diaminodiphenyl disulphide with β-naphthol.*

The disulphide (III) is certainly not produced by direct coupling of the tetrazonium salt with 2 moles of β-naphthol, as might superficially appear. This would not account (i) for the simultaneous formation of benzthiadiazole and *o*-(2-hydroxynaphthalene-1-azo)benzenesulphinic acid, or (ii) for the results of the coupling in sodium carbonate solution. In these more weakly alkaline conditions, the rate of degradation of the tetrazonium salt (II) would, if different, be slower than in aqueous sodium hydroxide. The formation of the disulphide would, therefore, be expected to be more complete, whereas, at most, traces are formed.

The reaction in sodium carbonate solution will proceed first as in sodium hydroxide, but the sulphenic acid (XXXI), being comparatively stable under these more weakly alkaline conditions, reacts with β-naphthol in preference to undergoing disproportionation and so yields the sulphide (X).

There is no report in the literature of the behaviour of sulphenic acids, their anhydrides or halides towards cold sodium carbonate solution as compared with sodium hydroxide, but we have established (i) that when the sulphenyl bromide (XX) in benzene is shaken with a 2% sodium hydroxide solution disproportionation occurs at once, whereas with a 2% sodium carbonate solution this is comparatively slow, and (ii) that in presence of β-naphthol only a very small amount (< 5%) of the sulphide (X) is formed in the former case and an almost quantitative yield in the latter.

Coupling in aqueous pyridine, sodium hydrogen carbonate, or sodium acetate is also initiated by the formation of the intermediate (XXX). However, in these weakly alkaline or acid conditions this product is sufficiently stable to allow coupling with a second mole of β-naphthol to take preference over degradation. Thus, only the disulphide (III) is formed. Although this is the most economical method for the preparation of this substance, the yields obtained (40—65%) and the isolation of small amounts of benzthiadiazole indicate that coupling is accompanied by a partial degradation of the tetrazonium salt.

Finally, it should be mentioned that the disulphide (III) is not stable to alkali, being converted, on prolonged contact at room temperature or on heating, into the sulphinic acid (IX). Undoubtedly this reaction is initiated by hydrolysis to the salts of 1-(*o*-mercaptobenzeneazo)-2-naphthol (IV) and the sulphenic acid (XXXI), which is a general reaction of disulphides (cf., *e.g.*, Schiller and Otto, *Ber.*, 1876, **9**, 1637; Fromm, *Annalen*, 1921, **426**, 313; Reissert and Manns, *Ber.*, 1928, **61**, 1308). Subsequently, (IV) is probably re-oxidised to the disulphide, and (XXXI) undergoes disproportionation to the disulphide and the sulphinic acid, which is, finally, the only product isolated.

The investigation is being continued in various directions.

EXPERIMENTAL.

Diazotisation of 2 : 2′-*Diaminodiphenyl Disulphide in Dilute Mineral Acids.*—The suspension of the amine hydrochloride obtained by intimate mixing of 2 : 2′-diaminodiphenyl disulphide (5 g.) and concentrated hydrochloric acid (20 c.c.) was poured into water (300 c.c.) at 0°. Sodium nitrite (4 g.) in a small amount of water was added. Benzthiadiazole and a brown resinous product, insoluble in water and ether, immediately separated. Extraction with ether yielded crude benzthiadiazole, m. p. 31—33° (m. p. when pure, 35°) (3·2 g., 58%). After filtration the aqueous layer was added to an alkaline solution of β-naphthol. 0·17 G. of an alkali-insoluble brown azo-compound separated. The experiment was repeated with sulphuric instead of hydrochloric acid and with increasing amounts of acid; the results were similar, yields of benzthiadiazole varying between 45 and 60%.

Diazotisation of 2 : 2′-*Diaminodiphenyl Disulphide according to Guha and Ghosh* (loc. cit.).—2 : 2′-Diaminodiphenyl disulphide (3 g.) and concentrated hydrochloric acid (7·5 c.c.) were mixed with mechanical stirring. The amine did not dissolve as claimed by Guha and Ghosh, but a suspension of the hydrochloride was obtained. This was cooled with ice, and a solution of sodium nitrite (1·8 g.) in water (15 c.c.) was added. An oil immediately separated, which soon solidified to a light-brown solid. When filtered off and washed with ice-cold water this melted at *ca.* 24°, solidifying again on cooling. No decomposition or evolution of nitrogen was observed. Steam-distillation of the precipitate yielded almost pure benzthiadiazole (m. p. 34—35°; 1·5 g., 46%).

Tetrazotisation of 2 : 2′-*Diaminodiphenyl Disulphide in Concentrated Sulphuric Acid.*—Sodium nitrite (3·6 g.) was slowly added with stirring to concentrated sulphuric acid (25 c.c.) at 0° and stirring continued for a further 10 minutes. The temperature was then raised to 70° during 20 minutes and the clear solution obtained was cooled to −10°. Powdered 2 : 2-diaminodiphenyl disulphide (5 g.) was dissolved in concentrated sulphuric acid (17 c.c.) at room temperature with vigorous stirring. After cooling to 0°, the solution was slowly added to the nitrosylsulphuric acid solution kept in a freezing mixture. The time allowed for diazotisation was varied between 10 minutes and 24 hours, with very little effect on the yields obtained in the following experiments. It was generally 30 minutes.

Action of Water on Tetrazotised 2 : 2′-*Diaminodiphenyl Disulphide in Concentrated Sulphuric Acid.*—The tetrazonium salt solution from the disulphide (5 g.) was poured into ice-water (800 c.c.). On extracting the solution immediately with ether, no benzthiadiazole was obtained. The solution with β-naphthol in aqueous sodium hydroxide gave the red precipitate of di-*o*-(2-hydroxynaphthalene-1-azo)-phenyl disulphide (III) recognised by its characteristic violet colour in benzene. After 30 minutes, crystalline benzthiadiazole began to separate and coupling as indicated above to decrease. After 4—6 hours, the solution ceased to yield any violet product with alkaline β-naphthol, indicating complete degradation of the tetrazonium salt. Extraction with ether yielded almost pure benzthiadiazole, m. p. 34—35° (4·0 g., 73%). The aqueous layer was poured into a solution of β-naphthol (3 g.) and sodium hydroxide (80 g.) in water (700 c.c.) at 0°. Alkali-insoluble, brown di-*o*-(2-hydroxynaphthalene-1-azo)phenyl sulphide (VIII) (0·5 g., 5%) was precipitated, which crystallised from xylene as reddish-orange needles, m. p. 284—286° (cf. below). The experiment was repeated, but the tetrazonium solution was kept at 0° up to 4 days before and after addition to water. The yields of benzthiadiazole and sulphide varied little.

Action of Aqueous Sodium Hydroxide, Sodium Carbonate, or Sodium Hydrogen Carbonate on Tetrazotised 2 : 2′-*Diaminodiphenyl Disulphide.*—A tetrazonium salt solution prepared from the disulphide (5 g.) was poured into ice-water (800 g.) containing sodium hydroxide (80 g.). Crude benzthiadiazole (2·7 g., 50%) separated immediately. The mother-liquor did not yield any azo-compound on subsequent quick addition of β-naphthol. Similar results were obtained when sodium hydroxide was replaced by sodium carbonate or sodium hydrogen carbonate.

Di-o-(2-*hydroxynaphthalene*-1-*azo*)*phenyl Sulphide* (VIII).—2 : 2′-Diaminodiphenyl sulphide (1·3 g.) was dissolved in concentrated hydrochloric acid (6 c.c.), glacial acetic acid (20 c.c.), and boiling water (100 c.c.). Sodium nitrite (0·85 g.) in a small amount of water was added at 0° and the mixture stirred for 10 minutes. The tetrazonium salt solution was poured into a solution of β-naphthol (3·5 g.) and sodium hydroxide (30 g.) in water (300 c.c.). The precipitated *sulphide* (2·8 g., 88%) was filtered off. It was obtained from xylene as reddish-orange needles, m. p. 284—286° (Found: N, 10·7; S, 5·9. $C_{32}H_{22}O_2N_4S$ requires N, 10·6; S, 6·1%).

Action of Cuprous Chloride on Tetrazotised 2 : 2′-*Diaminodiphenyl Disulphide in Concentrated Sulphuric Acid.*—A tetrazonium salt solution prepared from 5 g. of the disulphide was poured into an ice-cold solution of cuprous chloride (10 g.) in concentrated hydrochloric acid (90 c.c.), whereupon the brown *complex* (8·0 g.) of benzthiadiazole and cuprous chloride immediately separated (Found: Cu, 27·2. $2C_6H_4N_2S,Cu_2Cl_2$ requires Cu, 27·0%).

This experiment was repeated, but, without isolation of the complex, sodium hydroxide was added and the benzthiadiazole extracted with ether. The yield of almost pure product (m. p. 34—35°) was 4·6 g. (85%).

Coupling of Tetrazotised 2 : 2′-*Diaminodiphenyl Disulphide with β-Naphthol.*—(i) *Coupling in sodium hydroxide solution.* A solution of tetrazotised disulphide (5 g.) in concentrated sulphuric acid was slowly added to a solution of β-naphthol (6 g.) and sodium hydroxide (80 g.) in water (500 c.c.) and kept below 5° by the addition of ice (1·5 kg.). *Di*-(o-2-*hydroxynaphthalene*-1-*azo*)*phenyl disulphide* (III), contaminated by some benzthiadiazole and sodium sulphate separated. After 2 hours, the precipitate (3·3 g., 89%) was filtered off, washed with warm water and digested with methyl alcohol (100 c.c.). Crystallisation from benzene gives dark red needles (with a green lustre), m. p. 233—234°, containing one mole of benzene which is slowly lost at room temperature and quickly at 100° (in a vacuum) (Found: N, 10·3; S, 11·4. $C_{32}H_{22}O_2N_4S_2$ requires N, 10·0; S, 11·5%). This disulphide dissolves in organic solvents with a violet, and in concentrated sulphuric acid with an orange, colour.

The filtrate was treated with carbon dioxide. A red precipitate of sodium *o*-(2-hydroxynaphthalene-1-azo)benzenesulphinate (IX) separated, contaminated by β-naphthol. After filtration, washing with a small amount of water, and drying, it was digested with chloroform (100 c.c.) and collected. Yield: 2·1 g. (91%). M. p. 296° (decomp.). Acidification of an aqueous solution of the salt with hydrochloric acid yielded the reddish-brown crystalline free *acid*, m. p. 165—166°, sparingly soluble in water and alcohol and dissolving in concentrated sulphuric acid with deep violet colour (Found: N, 9·3. $C_{16}H_{12}O_3N_2S$ requires 9·0%).

Steam-distillation of the mother-liquor from the main reaction yielded almost pure benzthiadiazole, m. p. 34—35° (1·9 g., 70%).

(ii) *Coupling in sodium carbonate solution.* A sulphuric acid solution of tetrazotised 2 : 2′-diaminodiphenyl disulphide (5 g.) was slowly added to a well-stirred solution of β-naphthol (20 g.) in 5% aqueous sodium hydroxide (120 c.c.) and sodium carbonate (100 g.) in water (800 c.c.). After 2 hours, the precipitate of o-(2-*hydroxynaphthalene*-1-*azo*)*phenyl* 2-*hydroxy*-1-*naphthyl sulphide* (X), contaminated with sodium sulphate, β-naphthol, and benzthiadiazole, was filtered off, washed with hot water and digested with methyl alcohol (100 c.c.). Yield: 5·6 g. (66%). Crystallisation from xylene gives brownish-red needles, m. p. 226—227° (Found: N, 6·8; S, 7·8. $C_{26}H_{18}O_2N_2S$ requires N, 6·6; S, 7·6%). This compound is sparingly soluble in cold organic solvents and in hot aqueous hydroxide with a brown colour. Concentrated sulphuric acid dissolves it with a violet colour which rapidly becomes brown.

Steam-distillation of the main mother-liquor yielded almost pure benzthiadiazole, m. p. 34—35° (1·3 g., 48%).

(iii) *Coupling in sodium hydrogen carbonate, sodium acetate, or pyridine.* A tetrazonium salt solution prepared from 2 : 2′-diaminodiphenyl disulphide (5 g.) was dropped into a well-stirred slution of urea (3 g.) and sodium hydrogen carbonate (160 g.) in water (2000 c.c.) to which β-naphthol (30 g.) in alcohol (200 c.c.) had been added. The temperature was kept below 5° by the addition of ice. The precipitate of the disulphide (III) and β-naphthol was filtered off and digested twice with 3% aqueous sodium hydroxide to remove β-naphthol. The yield of crude *disulphide* (III) was 6·8 g. (61%). On steam-distillation of the mother-liquor 0·25 g. of benzthiadiazole was recovered. No sulphide (X) or sulphinic acid (IX) could be isolated from the alkaline extracts.

Similar results were obtained when sodium hydrogen carbonate was replaced by sodium acetate or pyridine. The yields of disulphide varied between 40 and 65%.

1-(o-*Methylthiobenzeneazo*)-2-*naphthol* (XI).—(i) *Preparation from the disulphide* (III). A suspension of (III) (0·5 g.) in methyl alcohol (40 c.c.) was shaken for 2 hours at room temperature with a solution of sodium sulphide nonahydrate (1 g.) in water (10 c.c.). Some dark violet, sparingly soluble sodium salt of 1-(*o*-mercaptobenzeneazo)-2-naphthol (IV) separated. Water (100 c.c.) was added to the suspension, followed by 4 additions of 10% aqueous sodium hydroxide (10 c.c. each) and methyl sulphate (0·35 g. each), with vigorous shaking. 1-(o-*Methylthiobenzeneazo*)-2-*naphthol* (XI), which separated almost pure in quantitative yield, crystallised from ethyl alcohol in red needles, m. p. 163—164° (Found: N, 9·8. $C_{17}H_{14}ON_2S$ requires N, 9·6%).

(ii) *Preparation from* o-*methylthioaniline.* To the aniline derivative (2 g.) in 10% hydrochloric acid (15 c.c.), sodium nitrite (1·1 g.) in a small amount of water was added at 0°. The diazonium solution was poured into a solution of β-naphthol (2·2 g.) in excess of aqueous sodium hydroxide. The red azo-compound formed was filtered off (Found: N, 9·7%) (2·2 g., 52%) and crystallised from ethyl alcohol in red needles, m. p. 163—164° undepressed by admixture with the product obtained as in (i).

1-(o-*Mercaptobenzeneazo*)-2-*naphthol* (IV).—A solution of sodium sulphide nonahydrate (2 g.) in water (10 c.c.) was added to a suspension of the disulphide (III) (1 g.) in ethyl alcohol (55 c.c.), and the mixture shaken for 4 hours at room temperature. Water (150 c.c.) was then added, and the sodium salt of 1-(*o*-mercaptobenzeneazo)-2-naphthol (0·75 g.) which separated in dark violet needles with a metallic bronze lustre was filtered off. By salting out the filtrate with sodium chloride a further 0·2 g. of less pure compound was obtained (total yield 0·95 g., 88%) (Found: N, 9·2; S, 10·2; Na, 7·5. $C_{16}H_{11}ON_2SNa$ requires N, 9·3; S, 10·6; Na, 7·6%).

On acidifying a suspension of the sodium compound (0·5 g.) in ethyl alcohol (50 c.c.) and water (200 c.c.) with concentrated hydrochloric acid (20 c.c.), 1-(o-*mercaptobenzeneazo*)-2-*naphthol* (IV) was obtained. When heated to 100° or crystallised from warm solvents, it was converted into a brown, alkali-insoluble product. Purified by concentration of its benzene solution at room temperature in a vacuum, it was obtained in red plates, sintering at about 115° and melting at 183—185° (Found: N, 10·1; S, 11·2. $C_{16}H_{12}ON_2S$ requires N, 10·0; S, 11·4%).

o-(2-*Hydroxynaphthalene*-1-*azo*)*phenyl* 2-*Methoxy*-1-*naphthyl Sulphide* (XIII).—(i) *Methylation of the* 2-*hydroxy*-1-*naphthyl sulphide* (X). Diazomethane (1·2 g.) in ether (200 c.c.) was added to the phenolic sulphide (2 g.) in dry benzene (400 c.c.). After 24 hours, the solvents were removed and the residue of *methoxy-sulphide* was recrystallised from benzene, forming red, monohydrated needles, sintering at about 125° and melting at 174—175° (Found: loss at 100°/15 mm., 4·2. $C_{27}H_{20}O_2N_2S,H_2O$ requires H_2O, 4·0%). After drying, the substance melts at 174—175° without sintering (Found: N, 6·5; S, 7·4; OMe, 6·9. $C_{27}H_{20}O_2N_2S$ requires N, 6·4; S, 7·3; OMe, 7·1%).

(ii) o-*Nitrophenyl 2-methoxy-*1-*naphthyl sulphide* (XV). A solution of *o*-nitrophenyl 2-hydroxy-1-naphthyl sulphide (Zincke and Farr, *loc. cit.*) (10 g.) in dry benzene (400 c.c.) was treated with diazomethane (3·6 g.) in ether (350 c.c.). After 24 hours the solvents were removed, and the residue, of almost pure *methoxy-sulphide* (XV) crystallised from benzene. It was obtained as yellow prisms, m. p. 174—175° (Found: N, 4·5; OMe, 9·5. $C_{17}H_{13}O_3NS$ requires N, 4·5; OMe, 9·9%).

(iii) o-*Aminophenyl 2-methoxy-*1-*naphthyl sulphide* (XVI). Stannous chloride dihydrate (12 g.) in concentrated hydrochloric acid (20 c.c.) was added at 100° to a solution of the above nitro-ether (5 g.) in glacial acetic acid (60 c.c.). After being heated on the steam-bath for 3 hours, the mixture was cooled. The precipitate of amino-sulphide stannichloride formed was filtered off, washed, and decomposed with 5% aqueous sodium hydroxide (200 c.c.). The free *amine* was collected and washed (2·6 g., 58%). Crystallisation from ethyl alcohol gave almost colourless plates, m. p. 136—137° (Found: N, 5·1; S, 11·2. $C_{17}H_{15}ONS$ requires N, 5·0; S, 11·4%).

(iv) *Coupling of diazotised* o-*aminophenyl 2-methoxy-*1-*naphthyl sulphide with β-naphthol.* The amine (0·5 g.) was dissolved in glacial acetic acid (12 c.c.) and concentrated hydrochloric acid (2 c.c.). After dilution with water (200 c.c.), sodium nitrite (0·15 g.) in a small amount of water was added at 0°. The diazonium solution was poured into a solution of β-naphthol (0·7 g.) and sodium hydroxide (12 g.) in water (100 c.c.). The red precipitate of *o*-(2-hydroxynaphthalene-1-azo)phenyl 2-methoxy-1-naphthyl sulphide (XIII) formed was filtered off, washed, and dried (0·78 g., 96%). It crystallised from benzene in red, hydrated needles, which sinter at about 125° and melt at 174—175° (Found: loss at 100°/15 mm., 4·5%). After drying they melt at 174—175° without sintering (Found: N, 6·5; S, 7·0; OMe, 6·9%). A mixed melting point with the dried product obtained as above showed no depression.

o-(2-*Hydroxynaphthalene-*1-*azo)phenyl Methyl Sulphone* (XVIII).—Sodium *o*-(2-hydroxynaphthalene-1-azo)phenylsulphinate (1 g.) was refluxed with methyl iodide (10 c.c.) for 6 hours. After cooling, the precipitate of *methyl sulphone* was filtered off, and washed repeatedly with 2% sodium hydroxide and finally with water. Crystallised from ethyl alcohol it formed brown needles, m. p. 184—185° (Found: N, 8·8. $C_{17}H_{14}O_3N_2S$ requires N, 8·6%).

p-*Nitrobenzyl* o-(2-*Hydroxynaphthalene-*1-*azo)phenyl Sulphone* (XIX).—The above-mentioned sodium sulphinate (2 g.) and *p*-nitrobenzyl bromide (2 g.) were refluxed in boiling ethyl alcohol (100 c.c.) for 30 hours. On dilution with water, a quantitative yield (2·7 g.) of p-*nitrobenzyl sulphone* was obtained. It crystallised from toluene in orange-red needles, m. p. 262—263° (Found: N, 9·6. $C_{23}H_{17}O_5N_3S$ requires N, 9·4%).

Conversion of the Sulphinic Acid (IX) *into the Disulphide* (III).—48% Hydrobromic acid (3 c.c.) was slowly added to a boiling suspension of the sulphinic acid (IX) (1 g.) in glacial acetic acid (25 c.c.). The solid went into solution. The cooled mixture was treated with water (400 c.c.). The disulphide (III) separated in quantitative yield (0·9 g.). Crystallisation from benzene gave a product, m. p. 233—234° alone or mixed with the product obtained by coupling tetrazotised 2 : 2′-diaminodiphenyl disulphide with β-naphthol.

Conversion of the Sulphinic Acid into o-(2-*Hydroxynaphthalene-*1-*azo)phenyl 2-Hydroxy-*1-*naphthyl Sulphide* (X).—(i) o-(2-*Hydroxynaphthalene-*1-*azo)phenylsulphenyl bromide* (XX). The sulphinic acid (IX) (2 g.), suspended in glacial acetic acid (50 c.c.) containing 48% hydrobromic acid (5 c.c.) and shaken for 48 hours at room temperature, slowly went into solution, and the *sulphenyl bromide* (XX) separated quantitatively as a fine dark-red crystalline powder. This was filtered off, washed with glacial acetic acid and finally with light petroleum. It melted at 184—186° (Found: N, 7·8; Br, 22·0. $C_{16}H_{11}ON_2BrS$ requires N, 7·8; Br. 22·3%).

(ii) *Condensation of the sulphenyl bromide with β-naphthol.* A mixture of the above sulphenyl bromide (0·5 g.) and β-naphthol (0·5 g.) was heated at 110—115°, hydrogen bromide being evolved and the liquid mass becoming gradually more viscous. After 15 minutes the reaction mixture was cooled and digested with methyl alcohol in order to remove the excess of β-naphthol. The insoluble residue consisted of almost pure *o*-(2-hydroxynaphthalene-1-azo)phenyl 2-hydroxy-1-naphthyl sulphide (0·55 g., 93%). Crystallisation from xylene yielded brownish-red needles, m. p. 226—227° alone or mixed with the product obtained by coupling tetrazotised 2 : 2′-diaminodiphenyl disulphide with β-naphthol in sodium carbonate solution.

Reaction of o-(2-*Hydroxynaphthalene-*1-*azo)benzenesulphenyl Bromide with β-Naphthol and Sodium Carbonate or Sodium Hydroxide Solution.*—(i) The sulphenyl bromide (0·5 g.) and β-naphthol (1·0 g.) in benzene (30 c.c.) were shaken with 2% aqueous sodium carbonate (40 c.c.) for 48 hours at room temperature. The aqueous layer contained only traces of coloured products. The benzene layer was washed with 3% aqueous sodium hydroxide and evaporated to dryness. The residue consisted of slightly impure sulphide (X) (0·46 g., 78%), which yielded a pure product m. p. 226—227°, after one crystallisation from xylene.

(ii) The experiment was repeated, but the sodium carbonate solution was replaced by 2% aqueous sodium hydroxide (30 c.c.). The benzene layer developed spontaneously the violet colour of the disulphide (III) which disappeared during the continued shaking. After 48 hours it contained only a small quantity (0·03 g.) of the crude sulphide (X). The aqueous layer was saturated with sodium chloride, whereupon sodium *o*-(2-hydroxynaphthalene-1-azo)benzene-2-sulphinate, m. p. 290° (decomp.), separated in almost quantitative yield.

Action of Sodium Hydroxide on the Disulphide (III).—The disulphide (0·5 g.) was refluxed for 3 hours with sodium hydroxide (2 g.) in aqueous ethyl alcohol (1 : 1; 40 c.c.). The solution obtained was diluted with water (50 c.c.) and extracted with benzene, from which a small amount of unchanged starting material (0·07 g.) was recovered. The aqueous layer was acidified with concentrated hydrochloric acid, and the precipitate of the sulphinic acid (IX), m. p. 164—166°, (0·44 g., 80%), collected.

Action of Sodium Hydroxide on o-(2-*Hydroxynaphthalene-*1-*azo)benzenesulphenyl Bromide.*—The sulphenyl bromide (0·5 g.), benzene (100 c.c.), and 2% aqueous sodium hydroxide (50 c.c.) were shaken at room temperature for 1 hour. The benzene layer was washed with dilute sodium hydroxide solution in order to remove small amounts of the sulphinic acid (IX) and finally evaporated to dryness. The residue consisted of almost pure di-*o*-(2-hydroxynaphthalene-1-azo)phenyl disulphide, m. p. 230—233° (0·25 g., 96%). The alkaline aqueous layer was treated with concentrated hydrochloric acid, and the precipitated sulphinic acid (m. p. 164—165°; 0·10 g., 69%), collected.

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94A. *Colouring Matters of the Aphididæ. Part II. Colouring Matters from* Aphis fabæ.

By J. P. E. HUMAN, A. W. JOHNSON, S. F. MACDONALD, and A. R. TODD.

An investigation leading to the isolation of four related colouring matters of a new type from the common bean aphid (*Aphis fabæ*) is described. The hæmolymph of the living insects contains the yellow *protoaphin*-fb, which is converted enzymically after the death of the insects into the fluorescent yellow *xanthoaphin*-fb. Protoaphin-*fb* can be isolated only from freshly collected insects which have been killed by a method (*e.g.*, quick heating) which simultaneously inactivates enzymes. Xanthoaphin-*fb* is unstable and undergoes ready conversion, particularly in presence of acids, first into the fluorescent, orange *chrysoaphin*-fb, and then into the fluorescent, carmine-red *erythroaphin*-fb. Preliminary chemical investigation of erythroaphin-*fb* indicates that it is a polycyclic quinone containing 2 phenolic hydroxyl groups; on oxidation with nitric acid it yields mellitic acid.

Very similar pigments are obtained from other species of Aphididæ, and the nomenclature adopted includes the use of suffix letters indicative of the species of origin.

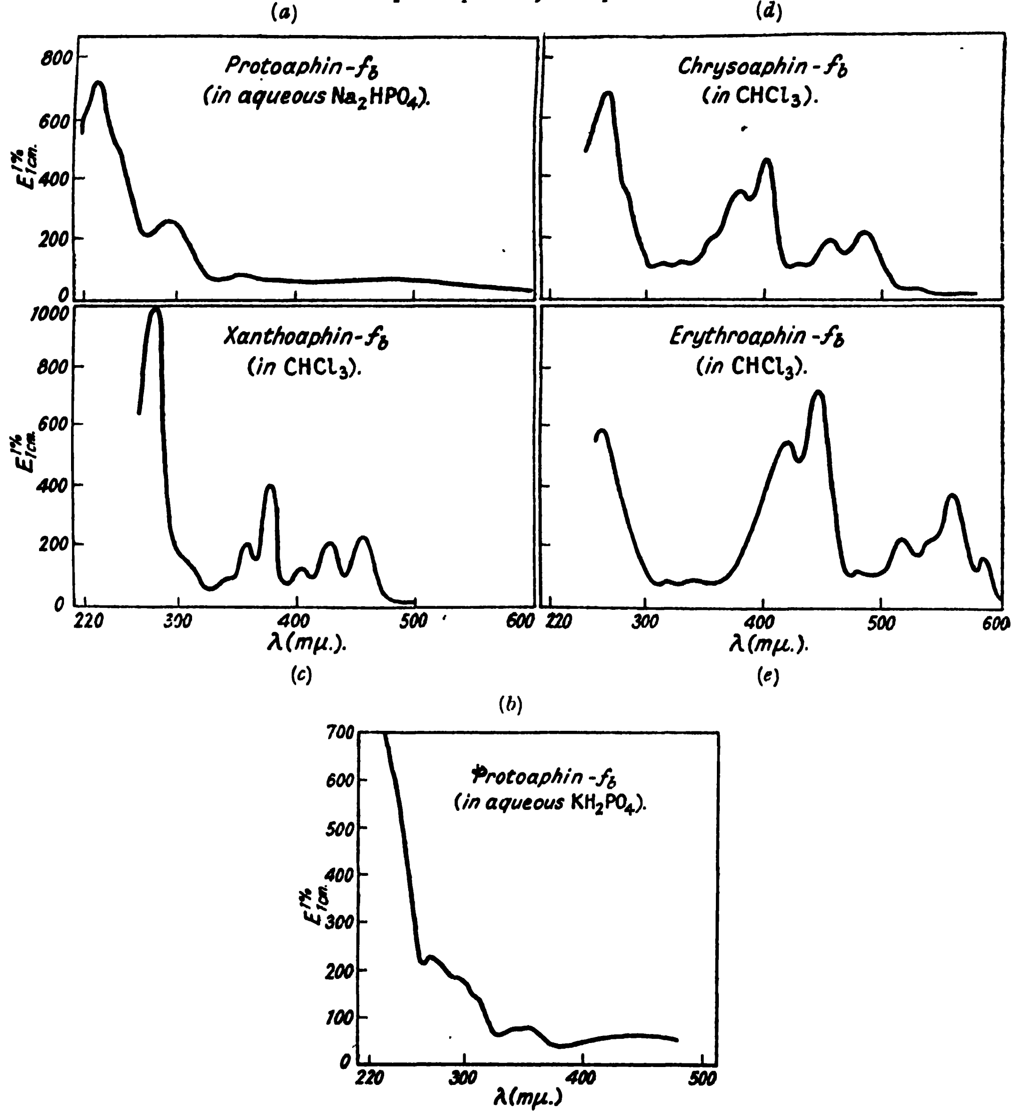
IN a preliminary communication (Duewell, Human, Johnson, MacDonald, and Todd, *Nature*, 1948, **162**, 759), which we regard as Part I of the present series of papers, we gave a general account of our initial investigations on a remarkable group of fluorescent colouring matters which occur in the hæmolymph of many species of Aphididæ, or which derive from precursors present in the hæmolymph. These pigments we propose to describe in general as *aphins*. In each species there are four aphins to be considered (*a*) the *protoaphin* present in the living insect, (*b*) the *xanthoaphin* into which protoaphin is converted by enzymic action on the death of the insect, (*c*) *chrysoaphin* produced when xanthoaphin is kept in solution, and (*d*) *erythroaphin* which is formed by a similar transformation of chrysoaphin and which represents the moderately stable end-product of the series. The conversions (*b*) ——> (*c*) ——> (*d*) occur spontaneously in crude extracts of the insects and appear to be independent of the presence of air, although they are enormously accelerated by heat or by acids or alkalis; the characteristic visible absorption spectra of the pigments make it easy to follow the conversions and to detect the individual pigments in solution by means of a hand-spectroscope. The existence of this series of pigments and their remarkable transformations were recorded in some detail by Sorby nearly eighty years ago (*Quart. J. Microscop. Sci.*, 1871, ii (N.S.), 352), but until now his work seems to have escaped the notice of other investigators. Thus Blount (*J.*, 1936, 1034) has reported the isolation of two aphid colouring matters lanigerin and strobinin (respectively a chrysoaphin and an erythroaphin on our nomenclature), and Schulz (*Biochem. Z.*, 1922, **127**, 122) has recorded some observations on the pigments of the woolly aphid (*Eriosoma lanigerum*) without apparently being aware of Sorby's pioneer work. Other colouring matters apparently unrelated to the aphins have also been detected by us in certain Aphididæ and will be described later; whether they are related to the pigments of *A. gossypii*, examined by Wall (*Ann. Entomol. Soc. Amer.*, 1933, **26**, 425), is at present unknown.

Although it is a simple matter to distinguish between the four aphins from any given aphid species by their visible and ultra-violet absorption spectra (cf. the spectra of the pigments from *Aphis fabæ* recorded in Fig. 1), it is not possible by this means to differentiate between the corresponding aphins from different species. Since, despite the close similarity in this and in many other respects, certain differences can nevertheless be detected in *X*-ray diffraction patterns and in infra-red absorption spectra, we have proposed that a two-letter suffix, indicative of the species of origin, be added to the name of each pigment until the question of identity or otherwise of corresponding pigments in the various species can be finally settled (Duewell, Human, Johnson, MacDonald, and Todd, *loc. cit.*). The present paper therefore deals with the isolation and preliminary examination of *protoaphin*-fb, *xanthoaphin*-fb, *chrysoaphin*-fb, and *erythroaphin*-fb, the pigments obtained from *Aphis fabæ*. This aphid is very prevalent in Britain and is the " black fly " which attacks cultivated broad beans (*Vicia faba*) during early summer with depressing regularity; it also occurs on a variety of other hosts, *e.g.*, members of the beetroot family. In our experiments the insect was obtained mainly from heavily infested, cultivated broad bean plants in Cambridgeshire.

Although the actual pigment content of *A. fabæ* is *ca.* 0·8% of the weight of live insects, the development of suitable methods for isolating the various aphins in a pure condition has been a slow and tedious matter. This was caused in part by our failure to appreciate at the outset of our researches that we were dealing with a group of very labile substances capable of undergoing the series of interconversions mentioned above, and in part to the necessity of devising methods whereby insects could be collected as far as possible alive and undamaged. An added complication was the difficulty of obtaining the large amounts of insects necessary and the development of methods whereby, since they are seasonal in habit, the collected insects could be stored for later study without gross decomposition of the aphins. It is not proposed to discuss in detail the various methods we have from time to time employed during the progress of the work;

Fig. 1.

Absorption spectra of the aphins-fb.



instead descriptions of methods will be confined essentially to those which we finally adopted for the isolation of the main bulk of *A. fabæ* pigments used in the present studies.

When undamaged specimens of *A. fabæ* are killed by quick heating to 70°, enzymes are simultaneously inactivated, and, if the insects are then crushed with aqueous acetone or aqueous methanol, extracts are obtained which show no characteristic bands in their visible-light absorption spectra and yield no fluorescent material on extraction with light petroleum. The colour of such crude extracts varies from red to greenish-brown in different batches of insects collected at different times. This is caused by the presence in the insects of varying amounts of a green material, apparently unrelated to the aphins. This green substance, which is probably a mixture of pigments, has not been closely examined, but its presence does not interfere with the isolation of the aphins; it is soluble in water, is unaffected by fermentation of the insect material, and is not extractable with light petroleum. When the filtered crude extracts are acidified and the acetone or methanol removed, protoaphin-*fb* separates as yellow needles. Protoaphin-*fb* contains only carbon, hydrogen, and oxygen, is yellow in acid aqueous solution and purplish-red at pH values >5·5. If, however, living specimens of *A. fabæ* are crushed with cold water and the suspension set aside at room temperature for an hour, the red colour of the protoaphin disappears and extraction of the resulting suspension with aqueous acetone gives bright yellow extracts with a strong bluish-green fluorescence. These extracts apparently contain no protoaphin-*fb*, since the yellow pigment they contain can be completely extracted from them with light petroleum; spectroscopic examination shows indeed that they contain mainly the water-insoluble xanthoaphin-*fb*. This conversion of protoaphin-*fb* into xanthoaphin-*fb* in crude extracts is best carried out by using, in place of water, buffer solution of pH 6·5. If the enzymic action occurs under unfavourable conditions, *e.g.*, on preserving dead but intact insects at temperatures > −10° for some weeks, the protoaphin-*fb* is degraded to various ill-defined products which can neither be extracted with light petroleum nor transformed into other aphins. Although the enzyme responsible for the conversion has not yet been isolated, there can be no doubt that protoaphin-*fb* is the precursor of xanthoaphin-*fb*. The crystalline protoaphin is converted into the xanthoaphin by treating solutions buffered to pH 6—7 with freshly crushed insects; under these conditions one crushed insect contains sufficient enzyme to convert some thirty times its own content of protoaphin. Again, although xanthoaphin-*fb*, chrysoaphin-*fb*, and erythroaphin-*fb* are all obtainable from dead fermented insects, they are not present to any appreciable extent in living insects. This follows from the facts that only protoaphin-*fb* is found in extracts of insects killed by being heated to 70° and that when living insects are crushed in concentrated sulphuric acid the solutions obtained do not show the strong absorption bands characteristic of the fluorescent aphins.

For the preparation of xanthoaphin, chrysoaphin, and erythroaphin, fermented insects are extracted with 80% acetone. Most of the fat in the extracts is separated by cooling and the solution is then shaken with light petroleum. Evaporation of the petroleum layer gives, as a rule, a granular precipitate of the mixed aphins in varying proportion, contaminated by some fat or wax which can be removed by re-extraction with light petroleum. Owing to the seasonal occurrence of *A. fabæ*, and indeed of all the Aphididæ, and the strictly limited period during which they can be collected in quantity, it was necessary to find some way of preserving the insects so that they could later be extracted. It has been found that this end can be achieved by storage at temperatures below −10° and that insects so stored for periods up to at least six months form suitable starting material for the preparation of chrysoaphin-*fb* and erythroaphin-*fb*, using a slight variation of the above method of extraction. For the xanthoaphin, fresh insects are preferable, and we have not been able to prepare protoaphin-*fb* in a pure state from preserved insects.

Separation and purification of the mixed aphins obtained by the above extraction procedures depend on the conversions xanthoaphin-*fb* ⟶ chrysoaphin-*fb* ⟶ erythroaphin-*fb* and on the fact that, although in most solvents the solubilities of the aphins decrease in the order named, this is reversed in carbon tetrachloride in which xanthoaphin-*fb* is the least soluble. The preparation of pure xanthoaphin-*fb* by direct crystallisation of the mixed aphins is satisfactory only when it is present in a relatively high proportion. It holds small amounts of solvents tenaciously and it is preferable to recrystallise it from ether immediately before analysis. Xanthoaphin-*fb* is unstable in solution or in the solid state in presence of light and changes into the orange chrysoaphin-*fb*; the change is greatly accelerated by heat or by acids, and it is advisable to carry out chemical manipulations with the substance rapidly and as far as possible in the absence of light.

Chrysoaphin-*fb* can be obtained by concentrating the carbon tetrachloride mother-liquor obtained after xanthoaphin has been separated from the crude mixed aphins. It may also be prepared from the yellow crystalline xanthoaphin by mild acid treatment, *e.g.*, by warming it with commercial chloroform; mixtures of xanthoaphin and chrysoaphin may be worked up for the latter by similar treatment. Like xanthoaphin-*fb*, chrysoaphin-*fb* has no definite melting point and on heating appears to undergo partial conversion into erythroaphin-*fb* before decomposing.

Erythroaphin-*fb*, which forms beautiful carmine-red needles, can be isolated from the final crystallisation mother-liquors of the mixed aphins. It can also be conveniently prepared from xanthoaphin-*fb* or chrysoaphin-*fb*, or from mixtures of these pigments, by warming their solutions in ethyl acetate with a little formic acid or by treating them in ethanolic solution with mineral acid. Purification of crude erythroaphin-*fb* is normally effected by recrystallisation from ethanol–chloroform; chromatography has not been found very useful, as the pigment is too strongly adsorbed on most of the common adsorbents.

Erythroaphin-*fb*, being the end-product and the most stable member of the aphin-*fb* series, was the most readily available material in the earlier stages of our work and has therefore been the subject of most investigation so far. Like the other aphins, it has no melting point and on heating it gradually chars and decomposes above 250°; it cannot be sublimed even in a high vacuum. It is moderately soluble in chloroform, carbon tetrachloride, benzene, or acetone, and only sparingly so in most of the other common organic solvents. In dry pyridine it dissolves readily but solutions in this solvent undergo some chemical change on storage. Solutions in organic solvents or in concentrated sulphuric acid are red and show a red fluorescence, which is particularly intense in ultra-violet light. Solutions in aqueous pyridine, sodium hydroxide, and ammonia are bright green and deposit green precipitates on storage, and similar solutions are obtained under certain conditions with sodium carbonate or hydrogen carbonate. On treatment with acetic anhydride containing a drop of sulphuric acid, the solution, at first red, changes rapidly through green to pure blue with an intense red fluorescence. This striking colour reaction was first described by Blount (*loc. cit.*) for strobinin (erythroaphin-*st*) and is characteristic of all the erythroaphins we have examined. Since under the acid conditions used, xanthoaphins and chrysoaphins are converted into the corresponding erythroaphins, it may be regarded as a general reaction for all the fluorescent aphins.

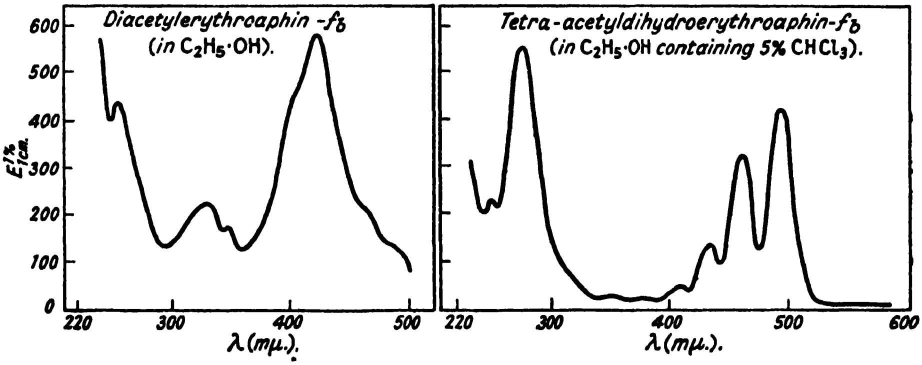
Erythroaphin-*fb* contains neither nitrogen, sulphur, nor halogens; it contains no methoxy-groups (Zeisel), and chromic acid oxidation (Kuhn–Roth) suggests the presence of several *C*-methyl residues. Difficulties have been encountered in obtaining consistent analytical values, but the results of a series of analyses indicate that it has a formula $C_{30}H_{22-24}O_8$. Attempts to determine the molecular weight of erythroaphin-*fb* by cryoscopic and ebullioscopic methods gave values ranging from 400 to 700, and similar inconsistent results were obtained using the Signer vapour-pressure method. Acyl derivatives of erythroaphin, although they seemed more suitable for these determinations on account of their greater solubility, also gave variable results. *X*-Ray crystallographic examination, however, indicates that erythroaphin-*fb* has a molecular weight of 260, 519, or 1038 ± 3% according to whether the unit cell contains 8, 4, or 2 molecules. Of these values only 519 ± 3% seems to be in accord with the behaviour of erythroaphin-*fb* on reduction and reductive acetylation and with the admittedly variable results of molecular-weight determinations by other methods. Acetylation yields *diacetylerythroaphin*-fb ($C_{34}H_{26-28}O_{10}$) which is insoluble in cold alkali and is readily hydrolysed to erythroaphin-*fb*. A *dibenzoyl* derivative has also been prepared, but attempted methylation failed to yield crystalline products. Hydrogenation of erythroaphin-*fb* in presence of a platinum catalyst or reduction with sodium dithionite gives a pale brown, fluorescent solution of a dihydroerythroaphin, which is rapidly re-oxidised in air to the original erythroaphin (identified by *X*-ray powder photography). These findings strongly suggest the presence of a quinonoid structure, and also the absence of non-reversibly reducing groups such as ethylenic linkages, aldehydo-groups etc. The presence of a quinonoid structure is confirmed by the behaviour of erythroaphin-*fb* or its diacetyl derivative on reductive acetylation, when the orange *tetra-acetyldihydroerythroaphin*-fb ($C_{38}H_{30-32}O_{12}$) is obtained. This derivative is insoluble in alkali and resists catalytic hydrogenation. Its formation eliminates a C_{15} formula for erythoaphin-*fb*, since reductive acetylation must introduce at least two acetyl groups. Evidence pointing to a C_{30} formula has also been obtained by quantitative microhydrogenation of erythroaphin-*fb* and its diacetyl derivative. A C_{60} formula (*i.e.*, *M*, 1038 ± 3%) would require the presence of two quinone groups and the absence of an intermediate absorption spectrum or of any break in the hydrogenation at the half-way stage is regarded as evidence against such a hypothesis. The absorption curves of diacetylerythroaphin-*fb* and tetra-acetyldihydroerythroaphin-*fb* are reproduced in Fig. 2.

In the erythroaphin-*fb* molecule, two oxygen atoms thus seem to be present in hydroxy-groups and two in a quinone system. The function of the remaining oxygens is still unknown, as is the nature of the nucleus. That the pigment is polynuclear would seem probable from the fact that oxidation with concentrated nitric acid yields mellitic acid, identified as its hexamethyl ester. In certain of its reactions erythroaphin-*fb* shows a resemblance to the photodynamic pigment of St. John's wort, hypericin, $C_{30}H_{16}O_8$ (Brockmann *et al.*, *Naturwiss.*, 1939, **27**, 550; *Annalen*, 1942, **553**, 1; Pace and McKinney, *J. Amer. Chem. Soc.*, 1941, **63**, 2570), and to the mould pigment oxypenicilliopsin (Oxford and Raistrick, *Biochem. J.*, 1940, **34**, 790). It is also of interest that Dhéré (*Compt. rend. Soc. Biol.*, 1939, **131**, 672; *Boissiera*, 1943, **7**, 423) has already remarked on the similarity between the ultra-violet fluorescence spectra of the lanigerin (chrysoaphin-*ln*) and strobinin (erythroaphin-*st*) of Blount (*loc. cit.*) and those of hypericin and oxypenicilliopsin. At present, however, there is insufficient chemical evidence to warrant any speculation on the nature of the relationship, if any, which may exist between erythroaphin-*fb* and these plant pigments.

So far little work has been done on the protoaphin, xanthoaphin and chrysoaphin from *A. fabæ*. The ready conversion of the last two into erythroaphin-*fb* complicates chemical study; thus, for example, when chrysoaphin-*fb* is acetylated the product is diacetylerythroaphin-*fb*. Elementary analysis gives values which correspond approximately to formulæ $C_{30}H_{30}O_{11}$ for xanthoaphin-*fb* and $C_{30}H_{26}O_9$ for chrysoaphin-*fb*. These formulæ, although only provisional, are at any rate in agreement with our failure to detect any by-products in the conversion of them into erythroaphin-*fb* and suggest that the conversion involves dehydration with an increase in aromatic character.

FIG. 2.

Absorption spectra of derivatives of erythroaphin-fb.



Protoaphin-*fb* differs from the three fluorescent aphins derived from it both in its chemical properties and in its composition. Analytical results suggest for it a formula $C_{36}H_{44}O_{19}$. It is reversibly reduced by dithionite to a colourless, fluorescent material, and it is readily oxidised to colourless products by a variety of reagents. Whether the enzymic conversion of protoaphin-*fb* to xanthoaphin-*fb* is accompanied by loss of a carbohydrate residue (as a comparison of the provisional formulæ of the compounds might suggest) has not yet been determined, and a decision on this and other relevant points must await the results of further work now in progress. It must be emphasised that the formulæ given in this paper for protoaphin-*fb*, xanthoaphin-*fb* and chrysoaphin-*fb* are advanced merely to indicate that a simple relationship between them and erythroaphin-*fb* would not conflict with the analytical data, and they may require considerable revision when further evidence becomes available.

EXPERIMENTAL.

Collection of Material.—After trial of a variety of methods, that which involved collection of the infected portions of bean plants and removal of the insects by a washing procedure (see below) was adopted for general use. Although it is possible to store *A. fabæ* at temperatures < −10° while still on the plants, it was found more satisfactory to remove them as soon as possible after the plants were collected and, after separating them from foreign insects, to keep the aphids in cold storage in glass bottles.

Protoaphin-fb.—Plant material bearing living insects was placed in a cylindrical basket of wire gauze (¼" mesh) which fitted inside a beaker (10-l. capacity) containing sufficient water (usually 6 l.) at 70° to immerse the plants completely. After 3 minutes the beaker and contents were placed in a sink lined with cotton gauze (cheese-cloth), and a strong jet of tap water was directed on one side of the basket. This had the effect of rotating the basket and washing the insects through the wire gauze, whereupon they passed out of the beaker with the stream of water and were collected on the cheese-cloth. After this operation, the beaker was removed and excess of water gently squeezed out of the insects before they were transferred to a beaker containing methanol (250 c.c. for each 100 g. of wet aphids).

The mixture of wet insects (100 g.) and methanol (150 c.c.) was ground in a Waring Blendor for 2 minutes. Hyflo Supercel (5 g.) was stirred into the suspension which was filtered through a thin layer of Supercel. The filter residue was again extracted with aqueous methanol (260 c.c. of 60%) in the Waring Blendor and filtered as before, and the combined extracts were diluted with an equal volume of methanol and extracted with light petroleum (b. p. 40—60°; 2 × 250 c.c.) to remove any traces of fluorescent aphins. The aqueous-methanolic layer was then concentrated under reduced pressure to 150 c.c., treated with active charcoal (6 g.; Darco G. 60) with stirring, and filtered. The filtrate at this point had pH *ca.* 5 and no longer became red at pH >7. The charcoal containing the adsorbed protoaphin-*fb* was thoroughly washed with water and eluted by being stirred with aqueous acetone (75%; 6 × 25 c.c.). On removal of the acetone from the eluate under reduced pressure, *protoaphin*-fb (0·25—0·5 g.) separated as small, flat, golden needles which were washed with water and dried. For further purification the product was dissolved in aqueous sodium hydroxide (N./100) and filtered, and the filtrate acidified to pH 4 with hydrochloric acid (N./100). The purified pigment had no m. p. and on heating gradually darkened and decomposed above 210° [Found, in material dried at 56°/0·1 mm.: C, 55·2; 55·8, 55·9; H, 5·8, 5·6, 5·6; active H, 1·41; *C*-CH$_3$ (Kuhn–Roth), 7·9. $C_{36}H_{44}O_{19}$ requires C, 55·4; H, 5·7%]. Protoaphin-*fb* contains neither nitrogen, sulphur, halogens, phosphorus, nor methoxyl. It is readily soluble in dilute sodium hydroxide solution, 70—80% acetone, or pyridine, moderately so in 80% ethanol, 80% acetic acid, or aqueous dioxan, and very sparingly soluble in water, ether, light petroleum, chloroform, ethanol, acetone, or acetic acid. Solutions in water and organic solvents, including anhydrous pyridine, are yellow and those in sodium hydroxide and aqueous pyridine purplish-red. In concentrated sulphuric acid the pigment dissolved with decomposition, the solution darkening rapidly. Light absorption: (i) In KH_2PO_4 solution: Maxima at 2730, 3530, and 4420—4450 A.; $E^{1\%}_{1\,\text{cm.}} = 220$, 73, and 62 with inflections at 2920—2960, 3000—3060, and 3450—3470 A.; $E^{1\%}_{1\,\text{cm.}} = 175$, 140, and 70 respectively. (ii) In Na_2HPO_4 solution: Maxima at 2340, 2960, 3560, and 5180 A.; $E^{1\%}_{1\,\text{cm.}} = 725$, 250, 75, and 70.

Xanthoaphin-fb.—The live insects were washed off infected bean plants as described under the preparation of protoaphin-*fb* (above), except that cold water was used throughout. The fresh wet aphids (150 g.) were crushed with Sörensen buffer (150 c.c.; pH 6·2) in a large mortar and left at room temperature for 1 hour. Acetone (600 c.c.) was then added and the mixture ground in a Waring Blendor for 2 minutes. After being stirred with Hyflo Supercel (5 g.) and filtered through Supercel, the residue was re-extracted with aqueous acetone (80%; 3 × 25 c.c.) until the extract was only faintly coloured. The combined greenish-brown filtrate and extracts were concentrated under reduced pressure, a "boiling stick" being used to promote even evaporation, until separation of solid on the surface set in, whereupon the mixture was cooled to −10° by addition of solid carbon dioxide. The precipitated fat was separated (Supercel) and the clarified solution extracted with light petroleum (b. p. 40—60°; 3 × 500 c.c.), emulsions formed during the extraction being readily broken by addition of small amounts of acetone. The combined petroleum extracts normally had a light-yellow colour and showed strong bluish-green fluorescence; they contained mainly xanthoaphin-*fb* with small amounts of chrysoaphin-*fb* and erythroaphin-*fb*. Solvent was removed at $\not>35°$ (bath-temp. $\not>50°$) under slightly reduced pressure, giving a pale brown residue of crude colouring matter (0·6—0·9 g.) which was normally free from all but traces of fat. The powder was washed with light petroleum, dried, and boiled with ether (80 c.c.). The ethereal extract was concentrated to smaller bulk (30 c.c.), acid-free carbon tetrachloride (30 c.c.) added, and the solution concentrated until crystallisation set in, whereafter it was cooled to 0°. The *xanthoaphin*-fb was collected and recrystallised from ether; it formed bright yellow needles (0·4 — 0·5 g.) which on heating did not melt but gradually decomposed above 210° (Found, in material dried at room temperature/0·1 mm. for 12 hours: C, 63·7, 63·5, 64·4, 64·3; H, 5·9, 5·5, 5·7, 5·9. $C_{30}H_{30}O_{11}$ requires C, 63·6; H, 5·3%). Qualitative tests for nitrogen, phosphorus, sulphur, and halogens were negative.

Xanthoaphin-*fb* is readily soluble in acetone, ethanol, pyridine, or ethyl acetate, moderately so in chloroform, ether, or benzene, and very sparingly in carbon tetrachloride or light petroleum; it is insoluble in water. Solutions in organic solvents or aqueous organic solvents at neutral or acid pH are bright yellow and show a bluish-green fluorescence even in daylight; in ultra-violet light the fluorescence is intense even for the solid substance. It dissolved readily in aqueous sodium hydroxide, giving a pink solution with a powerful yellowish-green fluorescence in ultra-violet light. Light absorption in chloroform: Maxima at 2820, 3580, 3780, 4050, 4290, and 4590 A.; $E^{1\%}_{1\,\text{cm.}} = 992$, 198, 400, 116, 205, and 228 respectively.

It is difficult to work with xanthoaphin-*fb* or at times even to purify it because of its great lability, particularly to traces of acid or to heat, under the influence of which it undergoes irreversible conversion into chrysoaphin-*fb* (see below). This conversion has frequently occurred during recrystallisation, presumably owing to the presence of unsuspected traces of acid. In the same way, crystalline xanthoaphin-*fb* is liable to undergo slow conversion on being kept for long periods in specimen tubes. Under favourable conditions extractions carried out as described above give xanthoaphin-*fb* in amounts greater than half of the crude aphin mixture. On the other hand, if preserved insects are used it is very difficult to isolate pure xanthoaphin-*fb* and in such cases it was usually better to employ a modified procedure, as described later, and to proceed directly to the isolation of the chrysoaphin and erythroaphin.

Chrysoaphin-fb.—The combined ether–carbon tetrachloride mother-liquors (40—60 c.c.) from the separation and crystallisation of the xanthoaphin-*fb* in the above experiment were heated under reflux with chloroform (20 c.c.; not specially purified and therefore slightly acidic) until the characteristic 4300-A. line in the visible-light absorption spectrum of the xanthoaphin could no longer be detected with the hand-spectroscope and was replaced by the 4860-A. band of the chrysoaphin. The solution was now concentrated until crystallisation began and then set aside for a short time. *Chrysoaphin*-fb (0·2—0·3 g.)

separated as minute orange crystals. Recrystallised from an acid-free mixture of chloroform and carbon tetrachloride, the substance had no definite m. p. but decomposed with darkening when heated above 250° (Found, in material dried at 60°/0·01 mm. for 14 hours: C, 68·0, 68·4, 68·2; H, 5·2, 4·8, 4·8; active H, 0·57. $C_{30}H_{26}O_9$ requires C, 67·9; H, 5·0%). Qualitative tests for nitrogen, phosphorus, sulphur, halogens, and methoxyl were negative. Light absorption in chloroform: Maxima at 2680, (3260), 3800, 4[illegible], (4300), and 4860 A.; $E^{1\%}_{1\,\text{cm.}}$ = 685, (101), 350, 454, (102), 190, and 213 respectively.

Chrysoaphin-*fb* is readily soluble in chloroform, acetone, dioxan, ethyl acetate, or pyridine, moderately so in ether, benzene, ethanol, or carbon tetrachloride, and sparingly in light petroleum; it is insoluble in water. Neutral or acidic solutions in organic solvents are yellow and have a blue-green fluorescence which is particularly brilliant when viewed in ultra-violet light. The substance dissolves in aqueous alkali to give a crimson solution with an intense orange fluorescence in ultra-violet light. The solid pigment itself has a fine orange fluorescence in ultra-violet light. Chrysoaphin-*fb* is converted into erythroaphin-*fb* on being heated with acids.

Erythroaphin-fb.—The combined mother-liquors from the chrysoaphin-*fb* preparation described above were evaporated under reduced pressure, the residue taken up in chloroform (50 c.c.), and formic acid (5 c.c.; anhydrous) added. The mixture was heated under reflux for 20 minutes, by which time examination of the solution with a hand-spectroscope revealed only the characteristic visible-light absorption bands of erythroaphin-*fb*. Most of the solvent was removed by distillation, warm ethanol (30 c.c.) was added, and the solution concentrated until crystallisation set in. Set aside overnight, *erythroaphin*-fb had separated as small deep-carmine-red needles (0·1 – 0·15 g.); for analysis it was recrystallised several times from chloroform–ethanol [Found, in material dried at 60°/0·01 mm. for 12 hours: C, 70·5, 70·6; H, 4·8, 4·6; active H, 0·84; C-CH$_3$ (Kuhn–Roth), 12·4. $C_{30}H_{22}O_8$ requires C, 70·6; H, 4·4. $C_{30}H_{24}O_8$ requires C, 70·3; H, 4·7%]. Erythroaphin-*fb* contains no halogens, nitrogen, phosphorus, sulphur, or methoxyl, and it has no definite m p., charring and decomposing above 250°. Light absorption in chloroform: Maxima at 2670, 4210, 4465, 4850, 5205, 5600, and 5860 A.; $E^{1\%}_{1\,\text{cm.}}$ = 586, 550, 721, 115, 244, 375, and 165 respectively.

Erythroaphin-*fb* is moderately soluble in chloroform or carbon tetrachloride, somewhat less so in pyridine, acetone, benzene, dioxan, ether, acetic acid, or acetic anhydride; it is very sparingly soluble in ethanol or ethyl acetate and quite insoluble in water. Neutral or acid solutions in organic solvents are red with an orange-red fluorescence which is intense in ultra-violet light. With sodium hydroxide it gives deep-green solutions with a ruby-red fluorescence visible in ultra-violet light. Although neither sodium carbonate nor hydrogen carbonate will extract erythroaphin-*fb* from its solutions in benzene or chloroform, sodium carbonate, but not hydrogen carbonate, will extract it from ether; again, if the pigment is first dissolved in a little acetone, ethanol, or dioxan, addition of either sodium carbonate or hydrogen carbonate will give the characteristic green solutions of the alkali salt, although neither of them in aqueous solution will dissolve the solid pigment. Erythroaphin-*fb* gives a red solution in concentrated sulphuric acid and with acetic anhydride containing a drop of sulphuric acid the initially red solution passes rapidly through green to blue and acquires a strong red fluorescence (cf. Blount, *loc. cit.*, on the same reaction with strobinin). Hydrogenation of the pigment (22·8 mg.) in dioxan solution with Adams's catalyst proceeded with uptake of 1·12 mols. of hydrogen (1·19 c.c. at 15°/754 mm.) calculated on a formula $C_{30}H_{24}O_8$, giving a pale brown solution with an intense green fluorescence. On exposure of the reduced solution to air it was rapidly re-oxidised, yielding the original erythroaphin-*fb*. A similar reversible reduction occurred with sodium dithionite.

Modified Extraction Procedure for Preserved Insects.—Since insects which have been preserved in cold storage are useless for preparation of protoaphin and since the isolation of the xanthoaphin was difficult, at any rate in the case of *A. fabæ*, a modified method of extraction has usually been employed in which only chrysoaphin-*fb* and erythroaphin-*fb* were isolated; the yields obtained varied considerably from batch to batch, as indeed they also did with different batches of fresh insects.

The preserved aphids (100 g.) were thoroughly extracted with acetone by the method described above in the preparation of xanthoaphin-*fb*, but the removal of fat by freezing was usually omitted. Any insoluble material was carefully removed before proceeding further, however, in order to avoid undue emulsification in the extraction of the aqueous-acetone solution with light petroleum (b. p. 40—60°; 3 × 250 c.c.). Evaporation of the orange-red petroleum extract left a viscous red oil which was freed from residual acetone under reduced pressure at room temperature. On boiling this oil with a small amount of light petroleum (b. p. 40—60°; 50 c.c.) for 10 minutes most of the fat was removed with little loss of colouring matter. The residue (0·4—0·5 g.), now a granular red powder, was washed with light petroleum and dissolved in chloroform (20 c.c.), carbon tetrachloride (50 c.c.) was added, and the solution concentrated until crystallisation set in. On cooling chrysoaphin-*fb* (75—150 mg.) separated. Erythroaphin-*fb* (50—100 mg.) was obtained from the chrysoaphin-*fb* mother-liquors by treatment with formic acid and working up as described above.

Enzymic Conversion of Protoaphin-fb *into the Fluorescent Derived Aphins.*—In the absence of a purified enzyme preparation, crushed insects were employed to bring about the conversion. A control experiment was first carried out in which preserved insects (10 g.) were crushed with water (2 c.c.), and the mixture set aside at room temperature for 18 hours and then ground with Hyflo Supercel (0·5 g.) and acetone (20 c.c.). The mixture was filtered and the residue thrice re-extracted in the same way with aqueous acetone (80%; 3 × 20 c.c.). The combined filtrates were extracted with light petroleum (b. p. 40—60°; 3 × 40 c.c.), and the extract was filtered and evaporated under reduced pressure. Fat was removed from the residue by digestion with light petroleum (25 c.c.), and the insoluble mixture of aphins was collected on a sintered-glass funnel, dried, and weighed. The result obtained gave an estimate of the weight of fluorescent aphins derived from the insects used. In subsequent experiments using varying amounts of insects, a weighed amount (*ca.* 60 mg.) of pure protoaphin-*fb* was dissolved in aqueous sodium hydroxide (N./100), the pH was adjusted to 5·8—6·2 by hydrochloric acid (*ca.* 5·6 c.c. of N./100), and the solution added to the insects about to be crushed; subsequent operations were carried out as above. It was found that the results were not materially affected by varying the amount of water used in the first crushing, but there was some variation according to the length of time the crushed insects were kept before extraction with acetone. For this reason, 18 hours was used as a standard time in the experiments recorded in the accompanying table. It is evident that one aphid contains enough enzyme to convert many times its own content of protoaphin-*fb* into the fluorescent aphins.

Wt. of insects (g.).	Wt. of added protoaphin-*fb* (mg.).	Total yield of aphins (mg.).	Wt. of aphins derived from insects (mg.).	Wt. of aphins derived from protoaphin-*fb* (mg.).
10	—	40·8	40·8	—
0·508	60·1	41·0	2·0	39·0
0·35	60·4	33·6	1·4	32·2
0·25	60·5	32·7	1·0	31·7

Diacetylerythroaphin-fb.—(*a*) *From erythroaphin*-fb. Acetylpyridinium chloride was prepared as a white semi-solid mass by dropwise addition of acetyl chloride (2 c.c.) to pure pyridine (5 c.c.) with shaking and external cooling. Erythroaphin-*fb* (200 mg.) dissolved in ice-cold pyridine (100 c.c.) was now added rapidly and the mixture stirred for 15 minutes and then allowed to come to room temperature; the initially red solution changed during this operation to a bright yellow semi-solid suspension. An equal volume of benzene was added, the mixture poured on ice, and the benzene layer washed thoroughly with water, hydrochloric acid, and again water, dried, and evaporated under reduced pressure. The resinous residue was dissolved in hot ethanol, and the solution concentrated to incipient crystallisation. On cooling, *diacetylerythroaphin*-fb separated as mustard-yellow needles. After two further recrystallisations from ethanol by a similar procedure the pure substance (190 mg.) melted with decomposition at 245—250° after previous darkening [Found: C, 68·5; 68·3; H, 4·5, 4·5; *O*-acetyl, 13·8, 14·2. $C_{30}H_{20}O_8(CO{\cdot}CH_3)_2$ requires C, 68·7; H, 4·4; *O*-acetyl, 14·5. $C_{30}H_{22}O_8(CO{\cdot}CH_3)_2$ requires C, 68·6; H, 4·7; *O*-acetyl, 14·4%). Light absorption in ethanol: Maxima at 2560, 3300, 3470, and 4245 A.; $E^{1\%}_{1\,\text{cm.}}$ = 428, 217, 167, and 566 respectively. Molecular weight by the freezing-point method in ethylene dibromide, 534 ($C_{34}H_{28}O_{10}$ requires *M*, 596).

Diacetylerythroaphin-*fb* appears to be dimorphous, since it was obtained on occasion as red prisms which were not closely examined but changed to the normal yellow form on recrystallisation. It is soluble in most of the common organic solvents with the exception of light petroleum, in which it is very sparingly soluble. Its yellowish-orange solutions in organic solvents fluoresce orange in ultra-violet light, and it is not extracted from such solutions by aqueous sodium hydroxide. Hydrolysis with ethanolic alkali yields erythroaphin-*fb*. Reduction with sodium dithionite or with hydrogen in presence of a platinum catalyst yields (in solution) a yellow product, rapidly re-oxidised to the original compound on exposure to air. Quantitative hydrogenation showed that the uptake of hydrogen during this reduction corresponds to 1 mol.

(*b*) *From chrysoaphin*-fb. Chrysoaphin-*fb* (108 mg.) was dissolved in cold dry pyridine (4 c.c.), acetic anhydride (4 c.c.) added, and the mixture kept in a stoppered flask for 12 hours at room temperature with occasional shaking. Benzene (100 c.c.) was added and the mixture washed with water (3 × 100 c.c.), dilute hydrochloric acid, and again with water. Dried and evaporated, the benzene layer yielded a red gum, which on dissolution in ethanol followed by concentration of the solution furnished yellow needles of diacetylerythroaphin-*fb* (87 mg.), identical with the product obtained by method (*a*) above (Found: C, 68·7, 68·7; H, 4·8, 4·6; *O*-acetyl, 14·6%).

Tetra-acetyldihydroerythroaphin-fb.—Acetic anhydride (2 c.c.) and anhydrous sodium acetate (20 mg.) were added to a solution of erythroaphin-*fb* (28 mg.) in dioxan (2 c.c.), and the whole was shaken with hydrogen at room temperature and atmospheric pressure in presence of Adams's platinum catalyst; hydrogen uptake (1·35 c.c., 1·1 mols.) was complete in 18 minutes. The catalyst was separated, an equal volume of chloroform added, and the solution washed with dilute aqueous sodium carbonate. The chloroform layer was dried and concentrated to small bulk (5 c.c.), and hot ethanol (20 c.c.) added. The filtered solution was then concentrated until crystallisation set in and was set aside to cool. Recrystallisation of the product in the same way gave *tetra-acetyldihydroerythroaphin*-fb (28 mg.) as orange needles which charred but did not melt at <320°. The same product was obtained from diacetylerythroaphin-*fb* by hydrogenation of a solution in acetic anhydride using Adams's platinum catalyst followed by removal of the solvent, treatment with ethanol, evaporation, and crystallisation of the product as above described [Found: C, 66·6, 66·6, 66·8; H, 4·7, 4·9, 4·9; *O*-acetyl, 24·4, 25·3. $C_{30}H_{20}O_8(CO{\cdot}CH_3)_4$ requires C, 67·0; H, 4·7; *O*-acetyl, 25·3. $C_{30}H_{22}O_8(CO{\cdot}CH_3)_4$ requires C, 66·8; H, 5·0; *O*-acetyl, 25·2%]. Molecular-weight determination in ethylene dibromide by the cryoscopic method gave a value 740 ($C_{38}H_{34}O_{12}$ requires *M*, 682); the difficulty encountered throughout the aphin series in obtaining consistent values for molecular weights by the common methods leads us to regard this figure as of qualitative rather than quantitative value. The compound is soluble in chloroform (although solutions appear to decompose on storage), moderately soluble in benzene, and sparingly so in ethanol. The yellow solutions in organic solvents exhibit an intense green fluorescence in ultra-violet light. Tetra-acetyldihydroerythroaphin-*fb* is not extracted from such solutions by aqueous sodium hydroxide, nor is it reducible with sodium dithionite. Light absorption in ethanol containing 5% of chloroform: Maxima at 2520, 2785, (3400), 3560, (3865), 4110, 4350, and 4955 A.; $E^{1\%}_{1\,\text{cm.}}$ = 221, 547, (19), 21, (16), 43, 134, 322, and 443 respectively.

Dibenzoylerythroaphin-fb.—Erythroaphin-*fb* (23 mg.) was shaken with pyridine (4 c.c.), benzoyl chloride (0·2 c.c.), and a small crystal of benzoic acid for 15 hours, then warmed to 50° for a few minutes, and evaporated under reduced pressure. The solid residue was dissolved in ether–benzene (1 : 1), and the solution washed with hydrochloric acid, then with sodium hydrogen carbonate, and finally with water before drying (Na_2SO_4). The solution was evaporated, the residue dissolved in hot ethanol, and water added until a cloudiness appeared. On cooling, *dibenzoylerythroaphin*-fb separated as a light-brown amorphous powder (Found: C, 73·1; H, 4·4. $C_{44}H_{32}O_{10}$ requires C, 73·3; H, 4·5%). Molecular-weight determination by the cryoscopic method in ethylene dibromide gave a value 728, but ebullioscopic methods in chloroform gave inconsistent results ($C_{44}H_{32}O_{10}$ requires *M*, 720).

Nitric Acid Oxidation of Erythroaphin-fb.—Erythroaphin-*fb* (100·6 mg.) was heated on the steam-bath with concentrated nitric acid (4 c.c.) until evolution of brown fumes had almost ceased (2 hours), and the pale brownish solution was evaporated to dryness. The residue was again heated with nitric acid (3 c.c.) for 1 hour and then once more evaporated to dryness, and the residue boiled with water (3 c.c.) for 1 hour. Evaporation of the aqueous solution gave a semi-solid mass which was dissolved in methanol (5 c.c.) and treated with excess of ethereal diazomethane. The mixture was set aside overnight and then evaporated. The solid residue was dissolved in a mixture of benzene (2·5 c.c.) and *n*-pentane (2·5 c.c.) and put on a column of neutral alumina (3 g.). The column was washed with the same solvent and then eluted by washing with benzene containing increasing amounts of chloroform. The main bulk of product was located in the benzene–20% chloroform (30 c.c.; wt. of eluate 5·6 mg.; m. p. 183—184°) and benzene–40% chloroform (30 c.c.; wt. of eluate 9·2 mg.; m. p. 184—185°) washings. The material from these two fractions was combined, re-chromatographed in the same way, and furnished hexamethyl mellitate (13·8 mg.), m. p. 184—185°, unchanged by recrystallisation from aqueous methanol (Found: C, 51·1; H, 4·3. Calc. for $C_{18}H_{18}O_{12}$: C, 50·7; H, 4·3%). The m. p. of the ester was not depressed on admixture with authentic hexamethyl mellitate (m. p. 187°).

The benzene–75% chloroform washings (55 c.c.) of the first chromatogram above gave a crystalline material (5·6 mg.; m. p. 125—150°) which was probably impure hexamethyl mellitate, and washing the column finally with chloroform and methanol gave a resinous material (10 mg.) which was not identified.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 3rd*, 1949.]

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95. *Colouring Matters of the Aphididæ. Part III. Colouring Matters from* Tuberolachnus salignus.

By H. DUEWELL, A. W. JOHNSON, S. F. MACDONALD, and A. R. TODD.

The four aphin colouring matters *protoaphin*-sl, *xanthoaphin*-sl, *chrysoaphin*-sl, and *erythroaphin*-sl have been isolated from the willow-tree aphid, *Tuberolachnus salignus*. Although in most respects the aphins-*sl* are very similar in physical and chemical properties to the aphins-*fb*, the differences between them are sufficiently marked to warrant the conclusion that the pigments of the two series are not identical. A method for the purification of erythroaphins, depending on partition between chloroform and sulphuric acid of varying strengths, has been developed. Erythroaphin-*sl* has been converted into a *diacetyl* and a *tetra-acetyldihydro*-derivative, and from the products of its oxidation with nitric acid mellitic acid has been isolated.

PARALLEL with the investigation of the colouring matters of *A. fabæ* already described (Human, Johnson, MacDonald, and Todd, preceding paper) a study has been made of the large brown aphid, *Tuberolachnus salignus* (Gmelin). This insect parasitises willow trees, especially the white willow, *Salix alba*, on which it forms large colonies on the underside of the branches from late summer until the first severe frosts. It is a very suitable aphid for chemical study as its colonies are usually free of foreign insects, its pigment content (up to 2% of the live weight) is very high, and it is large enough to be easily dislodged from the willow branches by gentle tapping, so that it is readily obtained alive and undamaged without resort to the washing processes necessary with *A. fabæ* and other species. From *T. salignus* we have obtained a series of colouring matters exactly analogous to those from *A. fabæ*. Following the system of nomenclature which has been laid down elsewhere (Duewell, Human, Johnson, MacDonald, and Todd, *Nature*, 1948, **162**, 759), the *T. salignus* pigments isolated have been named *protoaphin*-sl, *xanthoaphin*-sl, *chrysoaphin*-sl, and *erythroaphin*-sl. Although very similar in many of their properties to the corresponding *A. fabæ* pigments, they are apparently not identical with them.

As in the case of *A. fabæ*, the living insects contain protoaphin-*sl* which can be obtained only if the insects are killed by a method (*e.g.*, heating) which simultaneously inactivates or destroys the enzyme system which brings about the protoaphin–xanthoaphin conversion. Preliminary fermentation of dead insects gives material from which xanthoaphin-*sl*, chrysoaphin-*sl*, and erythroaphin-*sl* in variable amount can be obtained. The pure aphins-*sl* undergo the same interconversions as do the aphins-*fb*, and the methods of extraction and isolation used for them are generally similar to those used for the aphins-*fb*. The virtual absence of any green pigment similar to that which occurs in extracts of *A. fabæ* makes it easier to observe colour changes in the earlier stages of the extractions and differences in detail arise from the greater stability of xanthoaphin-*sl* as compared with xanthoaphin-*fb*. Thus, although specimens of *T. salignus* which have been long in storage or have been improperly fermented require extraction with acetone to obtain the mixture of fluorescent aphins, fresh insects which have been carefully fermented at pH 6·5 yield xanthoaphin-*sl* almost exclusively, and this compound can be directly extracted with ether. The isolation of all the erythroaphin-*sl* present in insect extracts from which the xanthoaphin and chrysoaphin have been largely removed presents difficulty owing to the accompanying fatty material and other impurities. This difficulty has been overcome by the discovery that the erythroaphin can be quantitatively extracted from chloroform by 72% sulphuric acid, and from 64% sulphuric acid by chloroform. Provided that the chloroform used is free from alcohols and chlorine this method gives excellent results and it can be applied not merely to erythroaphin-*sl* but also to the erythroaphins of *A. fabæ* and other species. It cannot, of course, be applied to either xanthoaphins or chrysoaphins, since these are converted at once into erythroaphins under such acid conditions. Partition between organic solvents and strong acids has been employed in the purification of several natural colouring matters, *e.g.*, porphyrins (Willstätter and Stoll, "Untersuchungen über Chlorophyll," Berlin, 1913, p. 262), stercobilin (Watson, *Z. physiol. Chem.*, 1935, **233**, 39), and azulenes (Plattner, Heilbronner, and Weber, *Helv. Chim. Acta*, 1949, **32**, 574) and might well find more general application; we have found, for example, that it is possible to separate mixtures of hydroxyanthraquinones, *e.g.*, catenarin and cynodontin, by partition between chloroform and 80% sulphuric acid.

In colour and general reactions the four aphins-*sl* are very similar to the corresponding aphins-*fb* (preceding paper). In visible and ultra-violet absorption and in fluorescence they are virtually indistinguishable. Despite these facts, the two series do not appear to be identical. There are differences in solubility, behaviour on heating, and crystalline form, and *X*-ray diffraction photographs of the aphins-*sl* show definite differences from those of the corresponding aphins-*fb*. According to observations made by Dr. N. Sheppard, differences also occur in the infra-red absorption spectra. The most striking difference however is found in the xanthoaphins. While the chrysoaphins and erythroaphins of the two series give analytical values indicating that they might well have the same molecular formulæ, the two xanthoaphins are markedly different in their carbon content; moreover, in the course of experimental work xanthoaphin-*sl* has consistently seemed more stable than its counterpart from *A. fabæ*.

As in the *A. fabæ* series, most of the chemical work so far carried out has been on erythroaphin-*sl*. This pigment we believe has a formula $C_{30}H_{24}O_8$, the evidence being analogous to that adduced in the case of erythroaphin-*fb* (preceding paper). Molecular-weight determinations by ebullioscopic methods gave variable results between 252 and 615 and *X*-ray crystallographic examination gave a value of 534 ± 5%, assuming 12 molecules per unit cell. Erythroaphin-*sl* is evidently quinonoid in nature and undergoes reversible reduction with sodium dithionite or with hydrogen in presence of a platinum catalyst, 1 mole of hydrogen being absorbed on the basis of a C_{30} formula for the pigment. Acetylation yields *diacetylerythroaphin*-sl and reductive acetylation *tetra-acetyldihydroerythroaphin*-sl.

Of the oxygen atoms in the erythroaphin-*sl* molecule, two are present in a quinone grouping and two in hydroxy-groups, which are probably phenolic in nature since the pigment can be extracted from organic solvents by aqueous sodium hydroxide giving a bright green precipitate. The function of the remaining four oxygen atoms is unknown. There is no evidence of carboxy-groups since neither diacetylerythroaphin-*sl* nor tetra-acetyldihydroerythroaphin-*sl* can be extracted from chloroform solution with dilute alkali. On the other hand, certain observations suggest the possibility that one or more lactonic or other latent acidic groups may be present. When a little sodium hydroxide is added to a solution of diacetylerythroaphin-*sl* in aqueous acetone, the colour changes from brownish-orange to green; this change does not involve deacetylation, since, if the green solution is quickly acidified, the original diacetylerythroaphin-*sl* is recovered unchanged. Similar treatment of tetra-acetyldihydroerythroaphin-*sl* with alkali under conditions which do not remove the acetyl groups gives a colour change yellow–red. Again, treatment of erythroaphin-*sl* in ethanol–dioxan solution with anhydrous hydrogen chloride gives a deep-green product, and addition of ethanol to the red solution of erythroaphin-*sl* in concentrated sulphuric acid causes a colour change to green.

In its behaviour towards bases erythroaphin-*sl* shows properties analogous to those described by Scholl (*Ber.*, 1941, **74**, 1129, 1171, 1182) in the hydroxyanthraquinone group. In dry pyridine it dissolves to a red solution, but in aqueous pyridine its solutions are green. Addition of excess of dry pyridine to the aqueous solution brings about a change from green to red. In general, erythroaphin-*sl* dissolves in tertiary bases to give red solutions which become green on addition of water, whereas in many primary and secondary amines (aniline is an exception) the solutions are green and are unaffected by water. We have also observed that hypericin behaves in a similar manner with bases.

As to the nature of the nucleus in erythroaphin-*sl* little is known. It evidently contains a fully substituted aromatic ring, since oxidation with nitric acid gives mellitic acid, just as it does with erythroaphin-*fb*. Other methods of oxidation did not yield identifiable products in preliminary experiments and zinc-dust fusions or distillations gave fluorescent oils, evidently mixtures of hydrocarbons, from which no solid products were isolated.

Very little work has yet been done on the other aphins from *T. salignus* and it is not yet possible to assign molecular formulæ to them with any certainty. On the assumptions that erythroaphin-*sl* has a molecular weight of 512 and that 1 mol. of xanthoaphin gives rise to 1 mol. of chrysoaphin and this in turn to 1 mol. of erythroaphin, the yields of the last-named pigment obtained in conversion reactions suggest that chrysoaphin-*sl* should have a molecular weight of $\ngtr$ 584, which would not conflict with a formula such as $C_{30}H_{26}O_9$. On the same basis, xanthoaphin-*sl* should have a molecular weight of $\ngtr$ 615 but it must be admitted that the surprisingly low hydrogen content (4·5%) found on elementary analysis makes it difficult to advance a formula bearing a simple relation to those of the others, as was possible in the case of the *A. fabæ* series (Human *et al.*, *loc. cit.*). Further examination of xanthoaphin-*sl* is clearly needed before any conclusions can be drawn. Since protoaphin-*sl* has been more superficially examined than the other *T. salignus* pigments, it is difficult to say whether the slightly lower carbon content observed as compared with protoaphin-*fb* is significant. It is at any rate clear that the pigments of the two series are very closely related to one another.

EXPERIMENTAL.

Unless otherwise stated, light petroleum refers to the fraction, b. p. 40—60°.

Collection of Insects.—Willow branches infected with *T. salignus* were carefully sawn into convenient lengths for handling and the insects dislodged from the undersides by gentle tapping and collected on Cellophane sheets. If not worked up immediately, the aphids so obtained were stored below −10° in glass bottles. Stored insects could not be used for the preparation of the protoaphin and were also unsatisfactory as raw material for the pure xanthoaphin. In the 1947 season some 900 g. of insects were collected and in 1948 *ca.* 450 g.; although by the final extraction methods up to 2% of mixed pigments can be isolated, losses were heavy in the earlier stages of our investigations and the total quantity of mixed aphins isolated was 11·9 g. Further losses were involved in separating the individual aphins from the mixture.

Protoaphin-sl.—The aphids (5 g.) were killed by plunging them into water at 80° for one minute. The dead insects were collected, washed with a little aqueous acetone (60%), and then extracted with the same solvent by grinding in a Waring Blendor for a few minutes. The mass was filtered and the filtrate (50 c.c.) thrice extracted with light petroleum, the volume being brought up to 50 c.c. after each extraction by addition of acetone. The filtered extract was concentrated until it began to foam, whereupon it was cooled and shaken with active charcoal (Darco G. 60; 0·25 g. and 0·5 g. in successive lots). Elution of the second lot of charcoal (0·5 g.) with aqueous acetone (75%), followed by concentration to small bulk and prolonged cooling, yielded *protoaphin*-sl (30 mg.) as small tan-coloured needles (Found: C, 54·5; 54·7; H, 5·8, 6·2%). No crystalline material was obtained from the elution of the first lot of charcoal. Protoaphin-*sl*, which has not been very closely studied as yet, is similar to protoaphin-*fb* (preceding paper) in all its properties. Its solutions are yellow in neutral or acidic conditions and purple-red in alkaline. Addition of fresh crushed aphids to an aqueous solution of protoaphin-*sl* buffered to pH 6·5 causes rapid conversion into xanthoaphin-*sl*.

Xanthoaphin-sl.—*Method* 1. Freshly collected *T. salignus* (100 g.) suspended in phosphate buffer (250 c.c.; pH 6·5) were pulped in a Waring Blendor and the insect sludge kept for 3 hours at room temperature before removal of fat by extraction with cold carbon tetrachloride (2 × 100 c.c.). The mixture of fluorescent aphins was then extracted with ether (5 × 100 c.c.), and the solvent was slowly distilled from the combined ethereal extracts. After the volume had been reduced to 150 c.c. it was maintained by slow addition of carbon tetrachloride (90 c.c.). The distillation of the resulting mixture was continued until the temperature of the vapour was 72°, whereupon the solution was set aside at room temperature for several hours. The *xanthoaphin*-sl (774 mg., 0·8%) which separated was purified by extraction from a thimble with acid-free ether, concentration to small bulk, and initiation of crystallisation by addition of pure carbon tetrachloride. It then formed bright yellow plates which had a yellow fluorescence in ultra-violet light and on heating darkened from *ca.* 170° and finally melted at 203—204° (Found, in material dried at room temperature: C, 59·9, 59·4, 59·6, 59·3; H, 4·4, 4·6, 4·3, 4·4. $C_{30}H_{26}O_{14}$ requires C, 59·1; H, 4·3%).

Because of the ease of conversion into chrysoaphin-*sl*, it is preferable to recrystallise not more than *ca.* 400 mg. at one time, and to store the solid pigment in the dark. Xanthoaphin-*sl* is very soluble in pyridine, acetone, ethanol, or ethyl acetate, moderately so in chloroform or ether, and sparingly soluble in cold benzene; it is very sparingly soluble in light petroleum or carbon tetrachloride. Solutions in organic solvents are yellow with a strong bluish-green fluorescence which is intensified in ultra-violet light. Alkaline solutions are pink with a green fluorescence when freshly prepared but, when kept, quickly change through crimson to green owing to progressive change to chrysoaphin-*sl* and erythroaphin-*sl*. Neutral solutions are more stable but the same changes occur on prolonged heating or if they are made acid. Light absorption in chloroform: Maxima at 2590, 2815, 3600, 3800, 4070, 4310, and 4590 A.; $E^{1\%}_{1\,\mathrm{cm.}}$ = 821, 880, 196, 394, 118, 189, and 205 respectively. The bands at 4310 and 4590 A. are easily detected with a hand spectroscope.

Method 2. Fresh *T. salignus* (80 g.) were suspended in phosphate buffer (200 c.c.; pH 6·5) and pulped in a Waring Blendor, giving a deep purplish-red sludge, which was left at room temperature for 1 hour, the colour changing to greenish-yellow. The sludge was extracted with light petroleum (200 c.c.) which removed most of the fat, together with a little of the pigment. Acetone (200 c.c.) was added to the insect sludge, the whole thoroughly stirred, and solid material removed by centrifugation; this solid was re-extracted in the same way with aqueous acetone (5 × 200 c.c. of 80%). The combined acetone extracts were then repeatedly shaken with light petroleum (11 × 200 c.c.), and the combined petroleum layers evaporated under reduced pressure (temp. ≯20°). The residue was diluted with light petroleum and again concentrated to small bulk (40 c.c.). The mixed aphins separated as a light-orange granular precipitate (1·4—1·7 g.) which was collected, washed with light petroleum, and dried at room temperature. The colouring matter remaining in the mother-liquor was later converted into erythroaphin-*sl* by treatment with formic acid (see below). The crude solid pigments (400 mg. at one time) were dissolved in acid-free ether by extraction from a thimble and the solution slowly distilled, carbon tetrachloride being added continuously until crystallisation set in. On cooling xanthoaphin-*sl* separated and was recrystallised from ether–carbon tetrachloride. In favourable cases the yield was about 40% of the weight of the crude pigments.

Chrysoaphin-sl.—This pigment was usually isolated from the mother-liquors of the xanthoaphin-*sl* prepared by Method 1 or 2 above, by further concentration and replacement of ether by carbon tetrachloride. The crude chrysoaphin so obtained (*e.g.*, 493 mg., 0·5% from 100 g. of insects by Method 1) was dissolved in chloroform and shaken with aqueous formic acid (10%) until the 4310-A. band of xanthoaphin-*sl* was no longer visible with the hand-spectroscope. The chloroform solution was then washed with water, dried, and evaporated. The residue was triturated with light petroleum and the granular *chrysoaphin*-sl collected and recrystallised from ether by extraction from a thimble followed by concentration of the solution. It formed small orange needles which fluoresce orange in ultra-violet light, m. p. 238—239° (decomp. with previous darkening) (Found, in material dried at 60°/0·01 mm. for 6 hours: C, 68·3, 68·2, 68·4; H, 5·0, 4·7, 5·0. $C_{30}H_{26}O_9$ requires C, 67·9; H, 4·9. $C_{34}H_{28}O_{10}$ requires C, 68·4; H, 5·0%). Light absorption in chloroform: Maxima at 3210, 3820, 4040, 4565, and 4850 A.; $E^{1\%}_{1\,\mathrm{cm.}}$ = 195, 419, 553, 206, and 253 respectively. The bands at 4850 and 4565 A. are readily detected with a hand-spectroscope. Chrysoaphin-*sl* is very souble in pyridine, soluble in chloroform, acetone, ethyl acetate, or benzene, sparingly soluble in carbon tetrachloride, ether, or ethanol and virtually insoluble in light petroleum. Solutions in organic solvents are yellow with a green fluorescence which in ultra-violet light becomes intense yellowish-green. Alkaline solutions are crimson but become green as conversion into a salt of erythroaphin-*sl* proceeds.

Erythroaphin-sl.—(i) *From chrysoaphin*-sl *mother-liquors*. The mother-liquors from the above chrysoaphin-*sl* preparation were evaporated, and the residue was dissolved in ethyl acetate (120 c.c.). Formic acid (20 c.c. of 85%) was added and the solution heated on the steam-bath for 5 minutes. On cooling, *erythroaphin*-sl (691 mg., 0·7% from 100 g. of insects) separated as dark red needles, m. p. 250—252° (decomp. with previous darkening), and was recrystallised from ether (extraction in a thimble) or from chloroform–ethanol (Found, in material dried at 60°/0·01 mm. for 12 hours: C, 70·2, 70·1, 70·1; H, 4·3, 4·3, 4·5. $C_{30}H_{24}O_8$ requires C, 70·3; H, 4·7. $C_{30}H_{22}O_8$ requires C, 70·6; H, 4·4%). Light absorption: (1) *In chloroform.* Maxima at 2555, 3195, 3335, 4215, 4470, 4855, 5200, 5600, and 5860 A.; log $\varepsilon_{\mathrm{max.}}$ 4·57, 3·65, 3·65, 4·49, 4·61, 3·77, 4·11, 4·30, and 3·90 respectively. (2) *In concentrated sulphuric acid.* Maxima at 2330, 2730, 2900, 4620, 5260, and 5680 A.; log $\varepsilon_{\mathrm{max.}}$ 4·66, 4·35, 4·27, 4·46, 4·28, and 4·55 respectively. (3) *In dioxan–*N/100-*sodium hydroxide* (1 : 1). Maxima at 2880, 4220, 4480, 5750, and 6215 A.; log $\varepsilon_{\mathrm{max.}}$ 4·70, 4·47, 4·56, 4·18, and 4·45 respectively.

Erythroaphin-*sl* is very soluble in pyridine or chloroform, soluble in carbon tetrachloride, acetone, or benzene, and sparingly soluble in ethyl acetate, ethanol, or light petroleum. Solutions in organic solvents are deep red with an orange fluorescence which is intense when viewed in ultra-violet light. The solid pigment has a dull red fluorescence in ultra-violet light. Solutions in sulphuric acid are red and show no fluorescence. With acetic anhydride containing a drop of sulphuric acid the solution passes through green to pure blue with an intense red fluorescence. Extraction of chloroform solutions of erythroaphin-*sl* with aqueous sodium hydroxide yields the insoluble green sodium salt at the interface.

Erythroaphin-*sl* is reversibly reduced by sodium dithionite or by catalytic hydrogenation, the reduced form being rapidly reoxidised in air. Quantitative hydrogenation with a platinum catalyst gave values of 487 and 495 for the molecular weight, assuming one quinone grouping per molecule. Ebullioscopic methods gave variable results (from 252—615) but *X*-ray crystallographic examination gave *M* 534 ± 5%, assuming 12 mols. per unit cell ($C_{30}H_{24}O_8$ requires *M*, 512).

(ii) *From crystalline chrysoaphin*-sl *or xanthoaphin*-sl. Chrysoaphin-*sl* (50 mg.) was dissolved in ethanol (50 c.c.) and concentrated sulphuric acid (0·3 c.c.) was added with shaking. The solution was set aside for 5½ hours and the erythroaphin-*sl* which separated was collected, washed with ethanol and light petroleum, and dried (yield, 43·7 mg.). Xanthoaphin-*sl* (50·1 mg.) treated in the same way also yielded erythroaphin-*sl* (41·7 mg.). The conversion of either pigment into erythroaphin-*sl* could also be brought about by heating it with ethyl acetate containing formic acid.

On the assumptions that the conversions are unimolecular and that erythroaphin-*sl* has a molecular weight of 512, the yields obtained in the conversions fix an upper limit for the molecular weight of chrysoaphin-*sl* at 584 and for xanthoaphin-*sl* at 615.

Purification of Erythroaphin-sl *by Partition.*—Crude erythroaphin-*sl* (1·018 g.), dissolved in alcohol-free chloroform (70 c.c.), was shaken with sulphuric acid (125 c.c.; 74%), whereupon the pigment passed into the acid layer. The acid solution was washed with chloroform (50 c.c.), then diluted with sulphuric acid (400 c.c. of 62%), and extracted with chloroform (6 × 50 c.c.); the red pigment passed into the chloroform, leaving a brownish aqueous-acid layer. The chloroform extracts were repeatedly washed with water, dried, and concentrated to small bulk under reduced pressure. Ethanol was added until turbidity appeared and the mixture was warmed to bring all into solution and set aside overnight, whereupon pure erythroaphin-*sl* separated.

Diacetylerythroaphin-sl.—Erythroaphin-*sl* (398 mg.) was dissolved in cold dry pyridine (50 c.c.), the solution cooled in ice, and acetyl chloride (8 c.c.) added dropwise with vigorous shaking, the temperature being kept below 10°. After the addition of acetyl chloride cooling was no longer necessary and the mixture was kept at room temperature for 15 minutes, by which time the initially red solution had changed to yellow. The solution was poured, with stirring, into ice-water, and the flocculent brown precipitate collected, washed with water, and dried; it then formed a brown amorphous powder (439 mg.). The crude product was extracted from a thimble with hot light petroleum–ether (1 : 1) during 2 hours and the separated material collected; a further quantity was recovered by evaporation of the solution. Further purification was effected by chromatography on a 1 : 1 talc–precipitated silica column (10 g.; 12 × 1·6 cm.). The diacetyl compound (218 mg.) in 50% benzene–light petroleum was brought on to the column and the solution forced through by application of pressure. The column was washed with more solvent until the eluate was colourless and then most of the solvent was removed from the combined eluate. *Diacetylerythroaphin*-sl was then precipitated by the addition of excess of light petroleum, being obtained as a light orange powder. It has been obtained crystalline only on one occasion so far and the analyses and determinations of spectra, etc., have mostly been carried out on amorphous material [Found: C, 68·8, 68·4; H, 4·6, 4·5; *O*-acetyl, 15·2, 13·5, 13·4%; *M* (ebullioscopic in chloroform), 572; (hydrogenation in dioxan over Pt), 593, 598. $C_{30}H_{22}O_8(CO{\cdot}CH_3)_2$ requires C, 68·4; H, 4·7; *O*-acetyl, 14·4%; *M*, 596). Diacetylerythroaphin-*sl* is very soluble in acetone, ethyl acetate, benzene, or pyridine, soluble in ether, alcohol, or methanol, sparingly soluble in light petroleum, and insoluble in water. Light absorption in chloroform (amorphous material): Maxima at 5870, 5360, 4920, 4280, 3490, 3330, and 2560 A.; log $\varepsilon_{max.}$ = 2·80, 3·34, 3·85, 4·55, 3·95, 4·07, and 4·42 respectively.

Tetra-acetyldihydroerythroaphin-sl.—(i) *Reductive acetylation of erythroaphin*-sl. Erythroaphin-*sl* (123 mg.), pure zinc dust (246 mg.), and anhydrous sodium acetate (25 mg.) were suspended in acetic anhydride (5 c.c.), and glacial acetic acid (1 c.c.) was added. The mixture was warmed and gently shaken until solution had been effected, and then heated under gentle reflux for 15 minutes. The reddish solution then showed a green fluorescence, and the completion of the reaction could be conveniently determined by adding a drop of the mixture to chloroform (1 c.c.) and shaking with water. When the chloroform solution stayed yellow, showing absorption bands at 4990 and 4670 A. (hand-spectroscope), and no re-oxidation took place in air, the solid material was separated from the hot reaction mixture, and the residue washed with hot acetic acid. The filtrate and washings were diluted with water, excess of acetic anhydride was hydrolysed, and the pale brown precipitate (151 mg.) separated, washed with water, and dried *in vacuo*. The crude acetyl derivative was dissolved in benzene (20 c.c.) and light petroleum (10 c.c.), and brought on to a 1 : 1 talc–precipitated silica column (10 g.; 11 × 1·6 cm.), and the solution forced through by application of pressure. The column was washed with light petroleum until the eluate was no longer coloured. The benzene addition *compound* of tetra-acetyldihydroerythroaphin-*sl* began to separate from the combined eluates after a few minutes (addition of more light petroleum if necessary), and after 12 hours the golden-yellow crystals of the benzene adduct were collected (123 mg.), m. p. 325° (decomp.). For analysis a sample was re-chromatographed and dried *in vacuo* at 60° (Found: C, 69·8; H, 5·1. $C_{38}H_{34}O_{12},C_6H_6$ requires C, 69·5; H, 5·3%). The benzene adduct was dissolved in chloroform (2 c.c.), and hot ethanol (25 c.c.) added. After 24 hours the orange platelets of *tetra-acetyldihydroerythroaphin*-sl were separated, washed with ethanol, and dried as above. The product darkened but did not melt below 320° (Found: C, 66·9; H, 5·1. $C_{38}H_{34}O_{12}$ requires C, 66·9; H, 5·0%). The tetra-acetyl compound is very soluble in pyridine and acetone, soluble in ethyl acetate, chloroform, or benzene, sparingly soluble in ether or ethanol, and insoluble in light petroleum. Light absorption in chloroform: Maxima at 2785, 4365, 4650, and 4980 A.; log $\varepsilon_{max.}$ = 4·56, 3·94, 4·30, and 4·43 respectively. Samples of the tetra-acetyl compound tend to deteriorate on storage, with the production of amorphous impurities, which, however, can be conveniently removed by chromatography on talc–precipitated silica columns as outlined above.

(ii) *Catalytic reductive acetylation of erythroaphin*-sl. Erythroaphin-*sl* (200 mg.), acetic anhydride (20 c.c.), anhydrous sodium acetate (50 mg.), and Adams's platinum catalyst (50 mg.) were hydrogenated at atmospheric pressure until no more hydrogen was absorbed. The catalyst was separated from the yellow solution, excess of ethanol added, and the mixture kept overnight. The solvent was removed under reduced pressure, the residue treated with water, and the crude acetyl compound separated, washed with water, and dried (250 mg.). The further purification was similar to that described in method (i). The acetyl compound was dissolved in 50% benzene–light petroleum and twice chromatographed on 1 : 1 talc–precipitated silica to yield the benzene addition product (175 mg.) (Found: C, 69·3; H, 4·9%). Recrystallisation from ethanol–chloroform gave pure tetra-acetyldihydroerythroaphin-*sl* [Found: C, 66·9; H, 4·7; *O*-acetyl, 24·8. Calc. for $C_{30}H_{22}O_8(CO{\cdot}CH_3)_4$: C, 66·9; H, 5·0; *O*-acetyl, 25·2%]. The absorption spectrum of the product was identical with that of the tetra-acetyl compound obtained by method (i). The catalytic reductive acetylation method is best for preparative purposes. In the absence of sodium acetate acetylation was incomplete.

(iii) *Catalytic reductive acetylation of diacetylerythroaphin*-sl. Diacetylerythroaphin-*sl* (216 mg.), acetic anhydride (15 c.c.), anhydrous sodium acetate (30 mg.), and Adams's platinum catalyst (50 mg.) were hydrogenated at atmospheric pressure until equilibrium was attained. The catalyst was separated, ethanol (45 c.c.) added, and the mixture kept overnight. The light-brown crystals were removed and a further crop (135 mg.) was obtained by concentration of the mother-liquors and addition of more ethanol. The crude material was purified by chromatography and crystallisation as described above

(Found : C, 66·7; H, 4·8; *O*-acetyl, 25·5%). The identity of the product with the previous preparations was also shown by comparison of the absorption spectra which revealed no differences.

Oxidation of Erythroaphin-sl with Nitric Acid.—Erythroaphin-*sl* (98 mg.) was warmed on the steam-bath with nitric acid (3 c.c.), a vigorous reaction setting in with copious evolution of nitrous fumes. The reaction soon subsided and the solution was heated for a further 2 hours. The reaction solution was transferred to a small flask and evaporated at 100° in a stream of air, leaving a pale yellow solid. Nitric acid (2 c.c.) was added, the solution again evaporated to dryness, and the process then repeated twice with water (2 c.c.) in order to remove any excess of nitric acid. The crude oxidation product was treated with excess of ethereal diazomethane, and the methylated material dissolved in benzene and put on a column of neutral alumina (5·4 g.). The chromatogram was washed with benzene, and then with benzene containing increasing amounts of chloroform. Those fractions which were obtained from the washings, up to benzene–40% chloroform, were crystalline (76·7 mg. in all), but the later runnings obtained with higher concentrations of chloroform and with chloroform–methanol mixtures were oily (70·6 mg.) and their nature has not been established. The combined crystalline fractions were re-chromatographed on neutral alumina (2·3 g.) with benzene–light petroleum (1 : 1) as solvent and elution with benzene–light petroleum (3 : 1). Recrystallised from aqueous methanol the product formed silky needles, m. p. 187—188° (Found : C, 50·9, 50·8; H, 4·7, 4·5. Calc. for $C_{18}H_{18}O_{12}$: C, 50·7; H, 4·3%). A mixed m. p. with authentic hexamethyl mellitate (m. p. 187—188°), kindly supplied by Dr. H. C. Howard of the Coal Research Laboratory, Pittsburgh, Pa., showed no depression.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 3rd, 1949.*]

96. *Acid-catalysed Hydration of Acraldehyde. Kinetics of the Reaction and Isolation of β-Hydroxypropaldehyde.*

By R. H. HALL and E. S. STERN.

A kinetic study of the acid-catalysed hydration of acraldehyde to β-hydroxypropaldehyde (hydracraldehyde; 3-hydroxypropan-1-al) in aqueous sulphuric acid confirms that the reaction is of the first order with respect to acraldehyde. The rate constants are independent of initial acraldehyde concentration, increase with increasing acid concentration, and are strictly proportional to Hammett's acidity function. β-Hydroxypropaldehyde, isolated (in poor yield) from the hydration media and characterised as the 2 : 4-dinitrophenylhydrazone, dimerises spontaneously to 4-hydroxy-2-2′-hydroxyethyl-1 : 3-dioxan, the unsymmetrical structure of which is proved by acetylation and hydrolysis. Representative kinetic experiments on the dehydration of β-hydroxypropaldehyde, using the dimer as starting material, demonstrate the ready reversibility of both the dimerisation of this aldehyde and the hydration of acraldehyde. A reversible mechanism proposed for the hydration of acraldehyde involves, as rate-determining step, the addition of a water molecule to the oxonium ion $CH_2{:}CH{\cdot}CH{:}OH^+$ and the simultaneous redistribution of the charge to give the oxonium ion $^+H_2O{\cdot}CH_2{\cdot}CH{:}CH{\cdot}OH$ which is the conjugate acid of the enol of β-hydroxypropaldehyde.

WITH the ready availability of acraldehyde on a commercial scale (see, *inter alia*, B.P. 569,625, 573,507, 600,454, 625,330; B.P. Appl. 22,712/39; Watson, *Chem. Eng.*, 1947, **54**, No. 12, 107), the preparation of β-hydroxypropaldehyde, an intermediate of great potential value in the solvent or the plasticiser field, has recently received considerable attention.

Although β-hydroxypropaldehyde may be prepared in several ways (cf. Nef, *Annalen*, 1904, **335**, 219; Glattfield and Sander, *J. Amer. Chem. Soc.*, 1921, **43**, 2675; Wohl and Schweitzer, *Ber.*, 1908, **41**, 3603; Stepanow and Schtschukin, *Chem. Zentr.*, 1927, I, 1167), most of the recent work has been concerned with the acid-catalysed hydration of acraldehyde (U.S.P. 2,434,110; German microfilmed reports PB 70,309, Frames 8214—8220; 73,508, Frames 7528—7537; and 19,417; G.P. Appl. D 89,752 IVd, Class o, 1943).

For the catalytic hydration processes described in the literature, conditions seem to be chosen rather arbitrarily and little systematic work appears to have been published in this connection. The kinetic data on the hydration of acraldehyde (Pressman and Lucas, *J. Amer. Chem. Soc.*, 1942, **64**, 1953), which are rather incomplete, are based on experiments with perchloric acid as catalyst and very dilute (about 0·03M.) solutions of acraldehyde, and are not, therefore, directly applicable to preparative work. A detailed kinetic study of the acid-catalysed hydration of acraldehyde was undertaken to provide fuller data, capable of such application, and an insight into the mechanism of the reaction, which has not hitherto been fully elucidated (cf. Hammett, " Physical Organic Chemistry," McGraw-Hill, 1940, p. 293).

In the present work the catalyst used for the hydration of acraldehyde between 20° and 50° was sulphuric acid in the concentration range 0·2—3·8N. The aldehyde concentration range studied was 0·138—2·76M. (*i.e.*, 1—20% v/v). In view of the possible polymerisation of acraldehyde in acid solution, it was decided to follow not only the rate of disappearance of the ethenoid unsaturation (by the bromine absorption method) but also the variations in the concentration of the carbonyl function (by an oximation procedure).

The presence of the acid catalyst, however, introduced large blank values into the analytical determinations of the carbonyl function and accurate values were difficult to obtain. Nevertheless, it was established that during the kinetic runs the aldehyde content of the media remained sensibly constant until after the equilibrium point of the hydration reaction had been reached. Prolonged reaction beyond this point, however, caused a diminution in the aldehyde concentration and it was concluded that a slow polymerisation was then occurring. It was also found that the rate of disappearance of aldehyde during this stage increased with increasing initial acid and acraldehyde concentrations. The fate of the aldehyde group during the polymerisation was not further investigated but it has been stated by Helberger (PB 19,417; FD 4806/47) that 3-formyl-Δ^3-dihydropyran is formed as hydration product. His claim that this is the sole volatile reaction product, however, is invalidated by the isolation of β-hydroxypropaldehyde from hydration media in the course of the present work (see below).

The kinetic data for the hydration of acraldehyde are collected in Tables I and II; the equilibrium concentration of acraldehyde was determined in each case and all kinetic runs were performed in duplicate. The equilibrium position was found to vary with temperature (cf. Pressman and Lucas, *loc. cit.*) and with the aldehyde concentration (Table II), higher conversions being achieved at lower temperatures and higher initial acraldehyde concentration; acid concentration was found to have no appreciable effect on the equilibrium position. The equilibrium constant K was calculated from the equation

$$K = \frac{\text{equilibrium concentration of }\beta\text{-hydroxypropaldehyde}}{\text{equilibrium concentration of acraldehyde}}$$

and the relationship $K = k_1/k_{-1}$ gave the ratio of the first-order rate constants of the forward and the backward reaction.

$$H_2O + CH_2{:}CH{\cdot}CHO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HO{\cdot}CH_2{\cdot}CH_2{\cdot}CHO$$

The sum of these rate constants corresponds to the overall rate constant k determined experimentally and defined (Hammett, *op. cit.*, p. 102) by

$$k = k_1 + k_{-1} = (2{\cdot}3/t)\log x_e/(x_e - x)$$

where x_e is the β-hydroxypropaldehyde concentration at equilibrium and x is that at time t.

TABLE I.

Effect of acid concentration and of temperature.

Initial acraldehyde concn. = 0·690M. throughout; k_1 = first-order rate constant of hydration; k_{-1} = first-order rate constant of dehydration; c_A = acid concentration; $K = k_1/k_{-1}$; H_0 = acidity function (values of Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721).

Temp.	H_2SO_4 concn. (N.).	$10^4(k_1 + k_{-1})$ (min.$^{-1}$).	10^4k_1 (min.$^{-1}$).	10^4k_{-1} (min.$^{-1}$).	Conversion at equilibrium (%).	K.	H_0.	$\log 10^4(k_1 + k_{-1}) + H_0$.	$\frac{10^4(k_1 + k_{-1})}{c_A}$.
20·0°	0·20	4·25	4·06	0·19	95·5	21·2	+1·26	1·88	21·3
20·0	1·00	22·5	21·5	1·0			+0·52	1·87	22·5
20·0	2·00	54·6	52·1	2·5			+0·12	1·86	27·3
20·0	3·80	152	145	7·0			−0·52	1·66	40
30·0	0·20	10·9	10·3	0·62	94·3	16·5	+1·26	2·30	54·5
30·0	1·00	57·8	54·5	3·3			+0·52	2·24	57·8
30·0	2·00	135	127	7·7			+0·12	2·25	67·5
30·0	3·80	350	330	20			−0·52	2·02	92·1
40·0	0·20	24·7	22·7	2·0	92·0	11·5	+1·26	2·65	124
40·0	1·00	133	122	11			+0·52	2·64	133
40·0	2·00	312	287	25			+0·12	2·61	156
40·0	3·80	855	787	68			−0·52	2·41	225
50·0	0·20	60·5	53·9	6·6	89·0	8·1	+1·26	3·04	303
50·0	1·00	305	272	33			+0·52	3·00	305
50·0	1·50	470	418	52			+0·32	2·99	313
50·0	2·00	665	592	73			+0·12	2·94	333

TABLE II.

Effect of acraldehyde concentration.

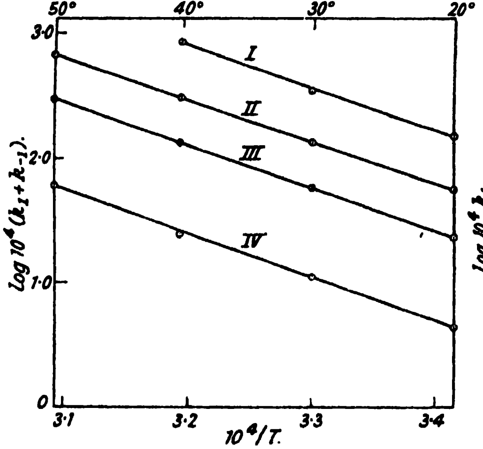
H_2SO_4 concn. is 1·00N. throughout.

Temp.	Initial acraldehyde concn. (M.).	$10^4(k_1 + k_{-1})$ (min.$^{-1}$).	10^4k_1 (min.$^{-1}$).	10^4k_{-1} (min.$^{-1}$).	Conversion at equilibrium (%).	K.
20·0°	0·138	22·9	21·3	1·6	92·9	13·1
20·0	0·690	22·5	21·5	1·0	95·5	21·2
20·0	1·38	22·7	21·9	0·8	96·5	27·6
20·0	2·76	20·6	20·0	0·6	96·9	31·3
50·0	0·138	303	255	48	84·0	5·25
50·0	0·690	305	272	33	89·0	8·1
50·0	1·38	297	271	26	91·1	10·2
50·0	2·76	269	250	19	93·1	13·5

It was found that the rate constants k and k_1 were independent of the initial acraldehyde concentration within the range 0·138—1·38M.; for 2·76M-acraldehyde solutions, however, the rate constants were lower by about 10% (Table II). This reduction is attributed to the changes in solvating and proton-donating properties of the reaction medium caused by the relatively high concentration of acraldehyde (~6 mol.-%), by analogy with the effect (cf. Braude *et al.*, *J.*, 1944, 443; 1948, 1982) of increasing concentrations of oxygenated organic substances in the reaction medium on the reaction rate and acidity function.

FIG. 1.

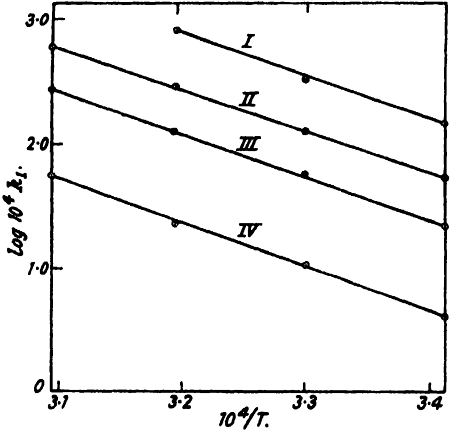
Arrhenius energy of activation.



Plot of "overall" k *against* 1/T.

FIG. 2.

Arrhenius energy of activation (hydration).



Plot of k_1 *against* 1/T.

Acid concns.: I, 3·8N.; II, 2·0N.; III, 1·0N.; IV, 0·2N.

The rate constants k increased with increasing acid concentration (Table I), but were not directly proportional to the stoicheiometric concentration of sulphuric acid, a relationship found by Pressman and Lucas (*loc. cit.*) to hold for 0·25N- and 0·5N-perchloric acid. Thus the ratio of k to c_A (Table I) increased greatly with acid concentration. The relation between k and acidity was accurately expressed for sulphuric acid concentrations between 0·20 and 2·00N. by Hammett and Deyrup's acidity function equation (*J. Amer. Chem. Soc.*, 1932, 54, 2721), *viz.*, $H_0 + \log k =$ constant, where H_0 is the acidity function, a measure of the tendency of the medium to donate a proton to a neutral base. For 3·8N-sulphuric acid the value of $H_0 + \log k$ was somewhat low.

Measurements at different temperatures showed that the rate constants k, k_1, and k_{-1} accurately obeyed the Arrhenius equation, the linearity of the log k–$1/T$ plots (Figs. 1, 2, and 3) being very marked.

The difference between the Arrhenius energies of activation (Tables III and IV) of the backward and the forward reaction (ΔE), *i.e.*, the heat of reaction, when 0·20—2·00N-sulphuric acid was used, was found to be 6·0 ± 0·2 kcals. per mol. This agreed closely with the value found by Pressman and Lucas (*loc. cit.*), *viz.*, 5·8 kcals. per mol., for ΔE under very different reaction conditions.

TABLE III.

Arrhenius energies of activation (in kcals./mol.).

Calculated from Table I. Initial acraldehyde concn. = 0·690M. throughout. Temp. range: 20·0—50·0°. $E = 2{\cdot}303 \times 1{\cdot}986 \times \frac{T_a T_b}{T_b - T_a} \times \log (k_b/k_a)$.

H_2SO_4 concn. (N.).	$E_{(k_1+k_{-1})}$.	$E_{(k_1)}$.	$E_{(k_{-1})}$.	$\Delta E = [E_{(k_{-1})} - E_{(k_1)}]$.
0·20	16·5	16·1	22·2	6·1
1·00	16·3	15·8	21·9	6·1
2·00	15·6	15·1	21·0	5·9
3·80	15·7	15·4	20·8	5·4

TABLE IV.

Arrhenius energies of activation (in kcals./mol.).

Calculated from Table II; H_2SO_4 concn. = 1·00N. throughout.

Initial acraldehyde concn. (M.).	$E_{(k_1+k_{-1})}$.	$E_{(k_1)}$.	$E_{(k_{-1})}$.	ΔE.
0·138	16·2	15·5	21·3	5·8
0·690	16·3	15·9	21·9	6·0
1·38	16·1	15·8	21·8	6·0
2·76	16·1	15·8	21·7	5·9

TABLE V.

Effect of mercuric sulphate.

Temp. = 50·0°; H_2SO_4 concn. = 1·00N.; initial acraldehyde concn. = 0·690M. throughout.

$HgSO_4$ concn. (% w/v)	nil	1	5	10
$10^4(k_1 + k_{-1})$ (min.$^{-1}$)	305	358	384	407

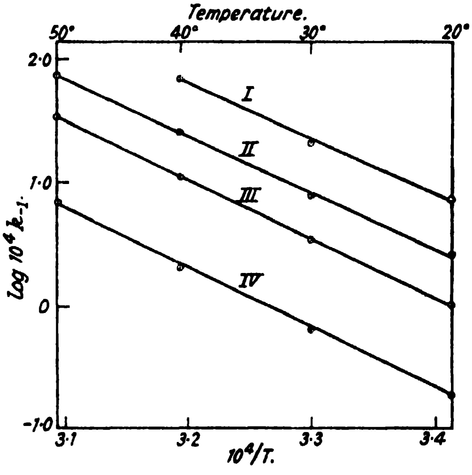
Addition of mercuric sulphate to the hydration mixture resulted in a considerable increase in the overall rate constant k (Table V); the rate of polymerisation of the aldehyde also appeared to be increased greatly, and solid deposits were observed in two runs before equilibrium had been attained.

Although the rate constants k and k_1 were independent of the initial acraldehyde concentration (see above) the rate constants k_{-1}, which were calculated by difference (Table II) and were much less accurate than the other rate constants, appeared to be appreciably affected by the initial acraldehyde concentration; in this connection it is noteworthy that the initial acraldehyde concentration also affected the equilibrium constants K, and these effects are probably related to the rapid reversible dimerisation of β-hydroxypropaldehyde which is discussed later.

The reversibility both of the dimerisation of the hydroxy-aldehyde and of the hydration of acraldehyde was proved in the course of kinetic experiments on the dehydration of the former. In view of its rapid dimerisation (see below) its dimer was used as the starting material for these experiments; in acid solution, under conditions exactly analogous to those under which the hydration had been studied, it was found that olefinic unsaturation appeared (*i.e.*, dehydration occurred) at an overall rate in satisfactory agreement with that of the hydration reaction; similar agreement was found for the equilibrium constants and for the energies of activation of the forward and the reverse reaction (cf. Experimental). The wide limits of error deemed "satisfactory agreement" are due to the inaccuracies inherent in the study of a reaction which reaches equilibrium at a conversion of less than 15%.

FIG. 3.

Arrhenius energy of activation (dehydration).



Plot of k_{-1} *against* $1/T$.

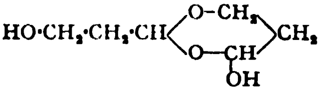
Acid concns.: I, 3·8N.; II, 2·0N.; III, 1·0N.; IV, 0·2N.

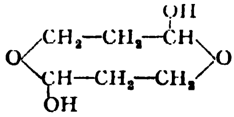
The isolation of pure β-hydroxypropaldehyde from the product of the acid-catalysed hydration had not previously been reported, and was thought by Helberger (PB 19,417) to be impracticable. In the present investigation it was found that after hydration at 50° for a time just sufficient to establish equilibrium and after careful neutralisation (pH 6—7) of the acid catalyst with solid calcium carbonate, 93% of acraldehyde had been converted and 96% of the initial aldehyde function remained in solution; the concentrate, obtained by passing the neutralised solution three times through a falling-film evaporator, contained about 10—20% water, and about 80—85% of the initial aldehyde function (by oxime determination). This concentrate was slowly distilled under oil-pump pressure at the lowest practicable bath temperature (cf. Glattfield and Sander, *J. Amer. Chem. Soc.*, 1921, **43**, 2675); in spite of these precautions, much resinification took place and the yield of pure β-hydroxypropaldehyde of b. p. 38°/0·2 mm. was low, amounting to a maximum of 20% of the theoretical weight.

The distillate, a comparatively mobile oil, was observed to become warm spontaneously within a few minutes of distillation, giving a viscous oil of n_D^{20} 1·4783, presumably the so-called " β-hydroxypropionaldehyde lactol " of Bergmann, Miekeley, and Lippmann (*Ber.*, 1929, **62**, 1467). By analogy (cf. Späth and Schmid, *Ber.*, 1941, **74**, 859) with acetaldol (which in our hands dimerised more slowly than β-hydroxypropaldehyde) this substance is now assigned the formula of the hemiacetal (I), and not the symmetrical formula (II) proposed by Bergmann *et al.* (*loc. cit.*).

The unsymmetrical structure (I) was shown to be correct by acetylation of the dimer by the method of Bergmann *et al.* (*loc. cit.*), and by hydrolysis of the diacetate with 0·05N-aqueous hydrochloric acid at 70° (cf. Späth and Schmid, *loc. cit.*), whereby it was found that the two acetyl groups were removed at different rates (Table VI). This, in conjunction with the hydrogenolysis of the diacetate to 2-2′-hydroxyethyl-1 : 3-dioxan (III), reported by Bergmann *et al.* (*loc. cit.*), may be accepted as conclusive proof of the unsymmetrical structure of dimeric β-hydroxypropaldehyde in accordance with the predictions of Späth and Schmid (*loc. cit.*) and of Owen (*Ann. Reports*, 1944, **41**, 139).

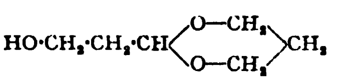
(I.)

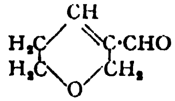




(II.)

(III.)





(IV.)

Reaction of the dimer of β-hydroxypropaldehyde with 2 : 4-dinitrophenylhydrazine in anhydrous methanol containing a little concentrated sulphuric acid rather surprisingly gave a high-melting derivative (m. p. 228°, decomp.), the ultra-violet light absorption of which was in agreement with that of an αβ-unsaturated aldehyde (cf. Braude and Jones, *J.*, 1945, 498). This compound was thought to be the 2 : *4-dinitrophenylhydrazone* of 3-formyl-Δ^3-dihydropyran (IV), a postulate supported by the elementary analysis. In view of the work reported by Helberger (PB 19,417), this material was not examined further but it is hoped that its identity may be established with certainty when details of Helberger's work become available.

In aqueous hydrochloric acid solution, dimeric β-hydroxypropaldehyde reacted with 2 : 4-dinitrophenylhydrazine giving a mixture of its own 2 : *4-dinitrophenylhydrazone*, together with that of acraldehyde and a little of the 2 : 4-dinitrophenylhydrazone, m. p. 228° (decomp.), obtained before.

This is a further confirmation of the fact that dimeric and monomeric β-hydroxypropaldehyde are in equilibrium in the solutions used, as is the case with the homologue, acetaldol (Späth, Lorenz, and Freund, *Ber.*, 1942, **75**, 1029); a further equilibrium is set up in acid solution between β-hydroxypropaldehyde and acraldehyde. The formation of the 3-formyl-Δ^3-dihydropyran may thus be explained by assuming a union of the two aldehydes, or a self-condensation of the former, and subsequent loss of water.

EXPERIMENTAL.

Materials.—Acraldehyde was fractionated before use through a 2-ft. glass column packed with single-turn glass helices; it had b. p. 51—52° and was stabilised by the addition of 0·2% (w/v) of quinol. Analysis both by oximation and by bromine absorption showed 92% purity; the remaining 8% was water.

Pure acraldehyde (100·3% by oximation; 99·4% by bromine absorption) was used in some runs which, however, gave kinetic results in close agreement with those obtained with 92% acraldehyde.

Kinetic Measurements.—The kinetic runs were carried out in 100 ml. of reaction medium in two-necked Pyrex flasks; one neck carried a double-surface condenser connected to a vent line. Samples were withdrawn through the other neck by means of calibrated, narrow-stem, rapid-delivery 1-ml. or 2-ml. or of calibrated bulb 5- or 10-ml. pipettes connected to a suction line. The reaction vessels were kept in a water tank, thermostatically controlled to within ±0·05° by a mercury–toluene bulb thermoregulator. All runs were carried out in duplicate.

To start a run the solution of the acid was rapidly added to the acraldehyde solution, both solutions having been pre-heated to the required temperature. The flask was vigorously shaken and a sample was taken from the homogeneous medium; the whole operation took less than 12 seconds. Four or five further samples and two equilibrium samples were analysed in the course of each run by the bromine absorption method, and two or three samples per run by the oximation method for aldehyde content.

The bromine absorption method (see below) of analysis gave very consistent results and the rate constants of any one run were generally within ±3%. Three runs in which the variation of rate constants exceeded ±5% were rejected and repeated. Duplicate runs then agreed to within ±3%. Average values of the duplicate runs are recorded in Tables I and II. Three typical runs are given below, titres being in ml. of 0·1N-sodium thiosulphate:

(*a*) 2·00N-H_2SO_4; 0·690M-acraldehyde; 20·0°.

Time (mins.)	0	30	60	91	122	155	620	900
Bromine absorption titre of 1·00 ml.	13·75	11·78	10·13	8·46	7·28	6·14	0·55	0·55
10^4k (min.$^{-1}$)	—	53·9	53·3	56·2	55·1	55·4	—	—

Concn. of acraldehyde at equilibrium: 4·0% of initial concn. 10^4k (average): 54·8 min.$^{-1}$.

(*b*) 2·00N-H_2SO_4; 0·690M-acraldehyde; 50·0°.

Time (mins.)	0	3	7	11	15	19	60	80
Bromine absorption titre of 1·00 ml.	12·46	10·49	8·48	6·70	5·46	4·40	1·35	1·37
10^4k (min.$^{-1}$)	—	648	637	668	662	680	—	—

Concn. of acraldehyde at equilibrium: 11·0% of initial concn. 10^4k (average): 659 min.$^{-1}$.

(*c*) 1·00N-H_2SO_4; 0·138M-acraldehyde; 20·0°.

Time (mins.)	0	60	121	180	301	1200	1520
Bromine absorption titre of 5·00 ml.	13·78	12·10	10·66	9·35	7·22	1·00	0·99
10^4k (min.$^{-1}$)	—	23·4	23·0	23·5	23·8	—	—

Concn. of acraldehyde at equilibrium: 7·2% of initial concn. 10^4k (average): 23·4 min.$^{-1}$.

The experimental conditions of the dehydration, carried out with dimeric β-hydroxypropaldehyde as starting material, were in every way analogous to those described above. In view of the low accuracy to be expected from these experiments, the following two runs only were performed (in duplicate), both with 1·00N-sulphuric acid and 0·065M-dimeric aldehyde (*i.e.*, 0·130M-β-hydroxypropaldehyde), titres being recorded as above:

(*a*) At 20·0°.

Time (mins.)	(i)	120	180	240	340	1440
Bromine absorption titre of 10·0 ml.		0·36	0·55	0·64	0·82	1·33
10^4k (min.$^{-1}$)		26·3	29·6	27·3	28·2	—
Time (mins.)	(ii)	125	180	240	334	1440
Bromine absorption titre of 10·0 ml.		0·37	0·54	0·66	0·79	1·33
10^4k (min.$^{-1}$)		26·1	28·9	28·5	27·1	—

Concn. of acraldehyde at equilibrium (% of initial aldehyde function): 5·2.
10^4k (average): (i) 27·9 min.$^{-1}$; (ii) 27·7 min.$^{-1}$.
$K = 18·2$; $k_1 = 26·4$ min.$^{-1}$; $k_{-1} = 1·4$ min.$^{-1}$.

(*b*) At 50·0°.

Time (mins.)	(i)	6	9	12	15	18	21	180
Bromine absorption titre of 10·0 ml.		0·47	0·75	0·93	1·09	1·29	1·38	3·19
10^4k (min.$^{-1}$)		265	298	287	278	288	270	—
Time (mins.)	(ii)	3	6	9	12	15	20	150
Bromine absorption titre of 10·0 ml.		0·24	0·45	0·71	0·91	1·13	1·28	3·19
10^4k (min.$^{-1}$)		261	253	279	280	291	256	—

Concn. of acraldehyde at equilibrium (% of initial aldehyde function): 12·4.
10^4k (average): (i) 281 min.$^{-1}$; (ii) 270 min.$^{-1}$.
$K = 7·0$; $k_1 = 241$ min.$^{-1}$; $k_{-1} = 34·4$ min.$^{-1}$.

Calculated Arrhenius energies of activation (in kcals./mol.):

$$E_{(k_1+k_{-1})}\ 14·4,\ E_{(k_1)}\ 13·9,\ E_{(k_{-1})}\ 20·1.\quad \Delta E = E_{(k_{-1})} - E_{(k_1)} = 6·2 \text{ kcals. per mol.}$$

Analytical Procedures.—(A) *Bromine absorption.* The sample was run into 20·0 ml. of standard (0·1N.) bromide–bromate reagent at 0°; after acidification with an excess of diluted (1 : 1) "AnalaR" hydrochloric acid, the mixture was kept at 0° for 30 seconds, treated with cold 20% w/v aqueous potassium iodide solution, diluted with 100 ml. of distilled water, and titrated with standard 0·1N-thiosulphate solution without indicator. Blank determinations were performed on the bromide–bromate reagent to permit calculation of unsaturation. Under the above conditions β-hydroxypropaldehyde was not brominated.

(B) *Oximation.* The sample was run into 50 ml. of neutral hydroxylamine hydrochloride reagent (20 g. of hydroxylamine hydrochloride per litre of approx. 90% ethanol, containing 25 ml. of 0·2% w/v alcoholic bromophenol-blue). After being heated (under reflux) on the steam-bath for 20 minutes, the solution was titrated at room temperature with 0·1N-sodium hydroxide solution. Blank determinations, performed under conditions identical but for the absence of hydroxylamine hydrochloride from the reagent solution, gave corrections for the acidity of the hydration mixture. Cf. Maltby and Primavesi, *Analyst*, **1949**, **74**, 498.

Preparation of β-Hydroxypropaldehyde.—A mixture of acraldehyde (75 ml.; purity 92%; 1 mol.), 3N-sulphuric acid (100 ml.), and water (325 ml.) was kept at 50° for 2·5 hours. The solution, the volume of which had decreased to 475 ml. (at room temp.), was rapidly cooled to 0°, and a sample was analysed; the acraldehyde conversion, determined by bromine absorption, was 93%, and the loss of aldehyde less than 1% (by oximation). Solid calcium carbonate was slowly added to the stirred solution until it was neutral (pH 6·8) to methyl-red (external indicator). After filtration under suction and thorough washing of the residue with distilled water, the solution (about 550—600 ml.) contained 96% of the initial amount of aldehyde function (by oximation).

The neutralised hydration medium was passed through a falling-film evaporator kept under vacuum (12 mm.); the evaporation surfaces were steam-heated, and the contact time was less than 20 seconds. The volume of liquid was reduced by about 40—50% per pass and generally three passes sufficed to remove about 85—95% of the water. The total loss of aldehyde function in these operations varied from 12 to 18%, 7%, presumably, being accounted for as unreacted acraldehyde.

The crude β-hydroxypropaldehyde (70—80 g.), containing about 15—25% of its weight of water and some polymeric material, was then distilled at the oil-pump under about 0·1—0·5 mm. The pure aldehyde (12—15 g.) distilled very slowly at 38—45°/0·2—0·5 mm. (Glattfield and Sander, *loc. cit.*, give b. p. 80—86°/14 mm.), and extensive resinification of the flask contents took place.

Dimeric β-Hydroxypropaldehyde (*4-Hydroxy-2-2′-hydroxyethyl-*1 : 3-*dioxan*).—The distillate from the above preparation became warm spontaneously and thickened to a viscous oil, n_D^{20} 1·4783, which was redistilled. Again, distillation proceeded slowly and some non-volatile, resinous material (2·5 g.) remained in the still. The distillate (10—12 g.), b. p. 40°/0·2 mm., n_D^{20} 1·4418, became warm spontaneously and gave the viscous dimer, n_D^{20} 1·4783 [Found: C, 48·95; H, 8·05; *M* (cryoscopic in dioxan), 152, 146. Calc. for $C_6H_{12}O_4$: C, 48·65; H, 8·15%; *M*, 148]. Oximation of the dimer by the procedure outlined above showed the presence of 1·99 potential carbonyl groups per mol., *i.e.*, the dimer behaved analytically as monomeric β-hydroxypropaldehyde.

2 : 4-*Dinitrophenylhydrazones.* (i) In anhydrous methanol. The dimeric aldehyde (1 g.) was dissolved in methanol (10 ml.) containing concentrated sulphuric acid (1 g.) and 2 : 4-dinitrophenylhydrazine (1·5 g.). After two days a solid (1·2 g.), probably 3-*formyl*-Δ^3-*dihydropyran* 2 : 4-*dinitrophenylhydrazone*, m. p. 214° (decomp.), had separated. After crystallisation from benzene containing 10% of ethyl acetate and chromatography on alumina (Peter Spence, type H) from benzene solution, it had m. p. 228° (decomp.) (Found: C, 49·35; H, 4·5. $C_{12}H_{12}O_5N_4$ requires C, 49·3; H, 4·15%), and light absorption maximum (in EtOH) at 3770 A., ε = 30,000.

(ii) In water. Dissolution of the dimeric aldehyde (1·5 g.) in a 2N-hydrochloric acid solution of 2 : 4-dinitrophenylhydrazine (2·5 g.) gave, within 5 minutes, a yellow precipitate (2 g.), m. p. 95—100°, which resolidified and then melted at 155—160° (decomp.). Chromatography of this material from benzene solution on alumina separated three substances: the most readily eluted was acraldehyde 2 : 4-dinitrophenylhydrazone (about 80 mg.), m. p. 161—162° (mixed m. p. with authentic material of m. p. 164° was 162—163°), light absorption maximum (in EtOH) at 3690 A., ε = 25,000 (Braude and Jones, *J.*, 1945, 498, give $\lambda_{max.}$ 3660 A., ε = 25,500). The intermediate benzene eluates contained slightly impure (?) 3-formyl-Δ^3-dihydropyran 2 : 4-dinitrophenylhydrazone (about 150 mg.), m. p. 217—219° (decomp.), light absorption maximum (in EtOH) at 3770 A., ε = 31,000. The most strongly adsorbed material was eluted with benzene–ethyl acetate (5 : 1) and consisted of *β-hydroxypropaldehyde* 2 : 4-*dinitrophenylhydrazone* (about 1 g.), m. p. 110°. This was once more chromatographed and then recrystallised from benzene. It finally had m. p. 132·5—133° (Found: C, 42·85; H, 4·25; N, 21·8. $C_9H_{10}O_5N_4$ requires C, 42·55; H, 3·95; N, 22·05%) and light absorption maximum (in EtOH) at 3600 A., ε = 24,000.

Structure of Dimeric β-Hydroxypropaldehyde.—The dimeric aldehyde (5 g.) was acetylated by the method of Bergmann *et al.* (*Ber.*, 1929, **62**, 1467) by being kept with acetic anhydride (10 ml.) and pyridine (10 ml.) at room temperature for 24 hours. Ether (150 ml.) was then added and the solution was washed with N-aqueous sodium hydroxide, N-aqueous hydrochloric acid, and, finally, water. The ethereal layer was dried and evaporated at 12 mm., leaving an oil (2·8 g.) which was fractionated. The product (2·1 g.), 4-acetoxy-2-2′-acetoxyethyl-1 : 3-dioxan, had b. p. 96°/0·1 mm., n_D^{20} 1·4489 (Found: C, 51·65; H, 7·4. Calc. for $C_{10}H_{16}O_6$: C, 51·7; H, 6·95%). Bergmann *et al.* (*loc. cit.*) give b. p. 122—123°/0·5 mm., n_D^{20}

TABLE VI.

*Hydrolysis of 4-acetoxy-2-2′-acetoxyethyl-*1 : 3-*dioxan by* 0·05N-HCl *at* 70·0°.

Time (mins.).	Titre (ml. 0·01N-NaOH).	Diff. from blank (ml.).	Acetyl groups hydrolysed.	Time (mins.).	Titre (ml. 0·01N-NaOH).	Diff. from blank (ml.).	Acetyl groups hydrolysed.
Blank	24·20	—	—	70	28·40	4·2	1·7(5)
0	26·05	1·85	0·7(5)	90	28·70	4·5	1·9
5	26·70	2·5	1·0(5)	110	28·85	4·65	1·9(5)
10	26·90	2·7	1·1(5)	120	29·0	4·8	2·0
20	27·20	3·0	1·2(5)	130	29·1	4·9	2·0(5)

1·4490. This diacetate was hydrolysed by the method used by Späth and Schmid (*Ber.*, 1941, **74**, 859) for the hydrolysis of acetaldol dimer diacetate: it (0·1114 g.), n_D^{20} 1·4489, was added to approximately 0·05N-aqueous hydrochloric acid (100 ml.) at 70·0° ± 0·3°. Samples (5 ml.) of the homogeneous solution were titrated against freshly prepared 0·01N-sodium hydroxide solution (phenolphthalein indicator). Boiled-out distilled water was used for the hydrolysis and titration. Results are given in Table VI.

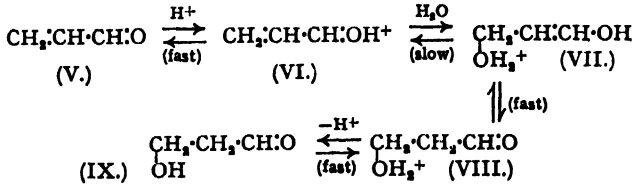
DISCUSSION.

Previous discussions of the mechanism of hydration reactions based on kinetic work have dealt largely with the hydration of reactive olefins (Lucas *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 460, 2138; cf. Hammett, *op. cit.*, p. 292) and it has been postulated that an intermediate carbonium ion is formed by interaction of the olefin with a solvated hydrogen ion. Evidence adduced in favour of this mechanism included the fact that the rate of hydration is of the first order with respect to both the hydrocarbon and the catalyst concentration, the proportionality of the reaction rate to acid concentration in mixtures at constant ionic strength, and the similarity of the effects of different strong acids.

The hydration of αβ-unsaturated carbonyl compounds was investigated by Lucas *et al.* (*J. Amer. Chem. Soc.*, 1937, **59**, 1461; 1942, **64**, 1122, 1953; 1944, **66**, 1818), and interpreted in the case of mesityl oxide, of acraldehyde, and of 3-methylbut-2-en-1-al in terms of two simultaneous reactions, a hydroxonium-ion-catalysed hydration of "uncomplexed," and to a less extent of "complexed" starting material, *i.e.*, hydration *via* a carbonium ion and an oxonium ion, respectively. Evidence put forward for this dual mechanism is the observed increase in the ratio of rate constant to acid concentration with increasing acid concentration (from 0·2 to 2·0N.); Lucas *et al.* appear to interpret this as an increased contribution of the oxonium-ion mechanism at higher acidities, although it is probably better ascribed to effects of the medium as represented by Hammett's acidity function.

The salient experimental facts emerging from the present work are: the hydration is an equilibrium reaction (the equilibrium being approachable from both sides) of the first order with respect to acraldehyde, the rate constants being independent of initial acraldehyde concentration within the range studied. The dependence of the rate constants (between 20° and 50°) on the acid concentration is accurately expressed by Hammett's acidity function (data for the temperature dependence of which are not available in the literature). This is a criterion for specific hydrogen-ion catalysis, in view of the non-proportionality of rate constants to stoicheiometric acid concentration (cf. Hammett *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 830; 1936, **58**, 2182; 1939, **61**, 2791). The Arrhenius energies of activation of the hydration and dehydration reactions determined experimentally are 15·7 ± 0·4 and 21·6 ± 0·6 kcals. per mol., respectively, over the wide range of conditions examined: the rate-determining step of the dehydration is therefore unlikely to involve the normal ionic or covalent fission of a carbon–oxygen bond, as the energy requirements for these would be higher. Moreover, the comparatively small difference (6·0 ± 0·2 kcals. per mol.) in these energies of activation (which is equal to the heat of reaction) makes it appear probable that both the hydration and the dehydration proceed through the same rate-determining step.

The following mechanism is in accord with the facts observed and the deductions listed above. The first step of the hydration reaction is the reversible, fast (cf. Braude, *J.*, 1944, 447; Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686), acid-induced transfer of a hydrogen ion from its solvate to the carbonyl group of acraldehyde (V) to give the oxonium ion (VI); during the next step, the rate-determining nucleophilic addition of a water molecule, the charge on the ion is redistributed, and the conjugate acid of an enol (VII) is produced which reverts to the carbonyl compound, the conjugate acid (VIII) of β-hydroxypropaldehyde; this tautomerisation would be expected to be fast (cf. Remick, "Electronic Interpretation of Organic Chemistry," J. Wiley and Sons, Inc., 1943, p. 376) and is therefore unlikely to constitute the rate-determining step. Fast reversible loss of a hydrogen ion from the conjugate acid finally affords β-hydroxypropaldehyde.



$$\underset{\text{(V.)}}{\mathrm{CH_2{:}CH{\cdot}CH{:}O}} \underset{\text{(fast)}}{\overset{H^+}{\rightleftharpoons}} \underset{\text{(VI.)}}{\mathrm{CH_2{:}CH{\cdot}CH{:}OH^+}} \underset{\text{(slow)}}{\overset{H_2O}{\rightleftharpoons}} \begin{matrix}\mathrm{CH_2{\cdot}CH{:}CH{\cdot}OH} \\ \mathrm{OH_2^+}\end{matrix}\ \text{(VII.)}$$

$$\text{(fast)}$$

$$\text{(IX.)}\ \begin{matrix}\mathrm{CH_2{\cdot}CH_2{\cdot}CH{:}O} \\ \mathrm{OH}\end{matrix} \underset{\text{(fast)}}{\overset{-H^+}{\leftrightharpoons}} \begin{matrix}\mathrm{CH_2{\cdot}CH_2{\cdot}CH{:}O} \\ \mathrm{OH_2^+}\end{matrix}\ \text{(VIII.)}$$

In the dehydration of this aldehyde the same steps are followed in the reverse order. The first is the fast acid-catalysed transfer of a hydrogen ion from the solvate to the aldehyde (IX); this will take place at the oxygen atom of the alcohol and not at that of the carbonyl group, as a carbonyl compound has stronger proton-donating (and thus weaker proton-accepting) properties than has an alcohol (cf. Braude *et al.*, *J.*, 1948, 1971, 1982). The oxonium ion (VIII) formed undergoes acid-catalysed enolisation (cf. Hammett, *op. cit.*, p. 231), generally a slow reaction (cf. Remick, *op. cit.*, p. 375) which in the case of the halogenation of carbonyl compounds constitutes the rate-determining step (Lapworth, *J.*, 1904, 85, 30; Bell, "Acid-Base Catalysis," Oxford, Clarendon Press, 1941, pp. 52, 69, 137); the rate of enolisation of acetone thus determined is, however, still about ten times as great as that of the dehydration of β-hydroxypropaldehyde under consideration here. Moreover, in the present case the charge on the oxonium ion (VIII) may be expected to facilitate tautomerisation, and it is thus most unlikely that the enolisation step is rate-determining in the dehydration of β-hydroxypropaldehyde. This makes it seem more likely that the rate-determining step is the loss of water from the enol (VII) which proceeds with a simultaneous redistribution of the charge to give the oxonium ion (VI), which on loss of a hydrogen ion affords acraldehyde (V).

The essential rôle of the acid catalyst is thus to permit the formation of the oxonium ions (VI and VII), interconversion of which involves the addition or loss of a neutral water molecule. This step will require less energy than the addition of one ion to, or its separation from, another. The formation of the enolic ion (VII) from the conjugate acid (VIII) of β-hyroxypropaldehyde in the dehydration reaction is presumably necessary as the olefinic link of the enol (VII) provides a ready means of charge distribution during the loss of the water molecule, and thus of forming the conjugated system of the ion (VI).

Several effects observed in the present work are not readily predictable on the basis of the mechanism proposed, although they are not excluded by it. They include the variation of the equilibrium constant K with temperature, and the effect of acraldehyde concentration on the equilibrium constant and on the rate constant k_{-1} (cf. Table II). Whilst the former variation may be explained thermochemically, the latter effects are probably due to the dimerisation of β-hydroxypropaldehyde, which is, however, readily reversible and does not prevent an approach to the equilibrium from the β-hydroxypropaldehyde side.

No difficulty was experienced owing to the polymerisation or cyclic condensation of the aldehydes in solution, and the constancy of the equilibrium values (taken after 6 and 8 half-times of reaction) provides good evidence that these undesirable side reactions are very much slower than the hydration of acraldehyde under the conditions here examined.

The authors are indebted to Dr. H. M. Stanley for his interest and encouragement, to Mr. R. J. R. Hayward for experimental assistance, to Mr. A. R. Philpotts for ultra-violet absorption data, and to the Directors of the Distillers Co. Ltd. for permission to publish this work. Micro-analyses are by Drs. Weiler and Strauss.

Research and Development Department,
The Distillers' Company Limited, Epsom, Surrey.
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97. *Equilibrium and Thermodynamic Relation in the Vapour-phase Catalytic Dehydration of Ethyl Alcohol to Ethyl Ether.*

By F. H. H. Valentin.

Equilibrium relations in the gas-phase dehydration of ethyl alcohol to ethyl ether have been studied. The thermo-dynamic functions for both the reaction and the substance ether have been derived. The values found for the heat content for ether are at variance with those previously accepted. Heat capacities calculated from spectroscopic functions agree with those derived from the experimental results.

In investigations on the formation of ether from alcohol it became necessary to find the requisite equilibrium and thermodynamic relations. For this we required suitable catalysts, a method of analysis for the reaction products, and a suitable apparatus for determination of the equilibrium constant.

Three groups of catalysts are known for the dehydration of alcohol to ether: aluminium oxide; aluminium sulphate; and sulphuric and phosphoric acids. A considerable number of alumina catalysts were investigated, but all were only slightly active at <250°, while at and above that temperature they formed ethylene as well as ether and were thus unsuitable for equilibrium determinations. An alum catalyst prepared according to Jatkar and Watson (*J. Soc. Chem. Ind.*, 1926, **45**, 168T) was found to lead to ether exclusively and in good yield at 200—240°. For equilibrium determinations at lower temperatures a new catalyst was developed consisting of sulphuric acid, promoted with copper sulphate, on a silica-gel carrier. This catalysed the formation of ether from alcohol exclusively, at 120—170°.

The product of the dehydration reaction was analysed by a method based on the fluoroboric-acid-catalysed reaction with acetic anhydride (Valentin, *J. S. African Chem. Inst.*, 1949, **2**, 59).

EXPERIMENTAL.

Preparation of the Sulphuric Acid–Copper Sulphate Catalyst.—Commercial silica gel was washed in a stream of water for 12 hours, then dried, and heated at 350° for 4 hours in a slow current of air. The gel (125 g.) was then soaked for 2 hours in a solution of sulphuric acid (12 c.c.) and copper sulphate (4·5 g.) in water (388 c.c.). The solution was decanted and the gel dried in an oven at 105° for 8 hours. The soaking and drying were repeated 4 times, all the solution being then taken up by the gel. The final drying was for 16 hours.

Apparatus for Equilibrium Determinations.—This consisted of a jacketed 4-l. steel autoclave containing the catalyst spread on two porcelain basins one above the other. Electric heating of the bottom kept a liquid boiling under reflux in the jacket at an accurately controlled low pressure. This ensured precise temperature control by virtue of the high heat transfer coefficient from a condensing vapour to a metal surface. Tetralin, used up to 170°, and "Dowtherm," used at higher temperatures, satisfactorily maintain their vapour pressure-temperature relations. The lid of the autoclave was heated electrically. The whole apparatus was well lagged and the temperature was the same (within ½°) at the bottom, centre, and top.

Equilibrium constants.

Temp., °K.	392	403	413	425	431	437	463	473	482
K_p (this work)	0·23	0·40	0·57	0·87	1·05	1·22	—	2·51	3·10
K_p (lit.)	—	8·0 [1]	—	—	—	—	2·3 [2]	—	—
Temp., °K.	492	498	503	509	523	539	542	548	
K_p (this work)	3·51	—	3·66	3·86	—	—	—	—	
K_p (lit.)	--	3·5 [3]	—	—	6·9 [4]	7·75 [5]	8·3 [7]	1·0 [1]	

[1] Pease and Yung, *J. Amer. Chem. Soc.*, 1924, **46**, 2397. [2] Mailhe and de Godon, *Bull. Soc. chim.*, 1916, **5**, 565. [3] Jatkar and Watson, *J. Indian Inst. Sci.*, 1926, **9**, *A*, 71. [4] Clark, Graham, and Winter, *J. Amer. Chem. Soc.*, 1925, **47**, 2748. [5] Newitt and Semerano, *Proc. Roy. Soc.*, 1936, **157**, *A*, 348. [6] Alvarado, *J. Amer. Chem. Soc.*, 1928, **50**, 790.

Procedure for Equilibrium Measurements.—The autoclave containing 100 g. of catalyst was brought up to the required reaction temperature and evacuated. Alcohol (30 c.c.) were pumped in with a controlled-volume pump, conditions were kept constant until equilibrium was attained, and two samples (*ca.* 2 g. each) were withdrawn at an interval of 15 minutes and totally condensed. The water formed in the reaction was adsorbed more strongly than the alcohol, causing a slight fall in pressure inside the autoclave as the reaction proceeded. Completion of the reaction was indicated by the pressure becoming constant, and was confirmed by the concordant analyses of the two samples. The total time required for the reaction varied from 6 hours at the lowest temperature to 2 hours at the highest.

Results.—The pressure in the autoclave was kept at *ca.* 3 atm. and, since in the reaction there is no change in the number of molecules, K_p was taken as equal to K_c within the limits of the experimental error. Results are given in the table.

The experimental results are represented by the empirical equation

$$\log K_p = 7{\cdot}70 - 2200T^{-1} - 1{\cdot}00 \log T \pm 0{\cdot}04$$

Thence other thermodynamic functions for the reaction were calculated, as follows:

$$\begin{aligned}\Delta F^\circ &= 10{\cdot}061 + 4{\cdot}573T \log T - 35{\cdot}21T \\ \Delta H^\circ &= 10{\cdot}061 - 1{\cdot}986T \\ \Delta C_p{}^\circ &= -1{\cdot}986 \\ \Delta S^\circ &= 52{\cdot}8 - 4{\cdot}55 \log T - 10{\cdot}020T^{-1}\end{aligned}$$

To minimise errors the following equation was used in calculating the entropy change

$$\Delta S^\circ = R\left(\frac{\mathrm{d} \log K_p}{\mathrm{d} \log T} + \log_e K_p\right)$$

DISCUSSION.

Thermodynamic data for ether are calculated from those for the reaction, the best available data for alcohol and water being used. For alcohol

$$\begin{aligned}C_p{}^\circ &= 3{\cdot}578 + 49{\cdot}847 \times 10^{-3}T - 169{\cdot}91 \times 10^{-7}T^2 \\ H^\circ &= -51{\cdot}762 + 3{\cdot}578T + 24{\cdot}924 \times 10^{-3}T^2 - 54{\cdot}64 \times 10^{-7}T^3 \\ S^\circ &= 31{\cdot}93 + 8{\cdot}239 \log T + 49{\cdot}85 \times 10^{-3}T - 84{\cdot}9 \times 10^{-7}T^2\end{aligned}$$

[from Spencer and Flanagan (*J. Amer. Chem. Soc.*, 1942, **64**, 2511), Brickwedde, Moskow, and Aston (*J. Res. Nat. Bur. Stand.*, 1946, **37**, 263), and Aston (*Ind. Eng. Chem.*, 1942, **34**, 514)].

For water

$$
\begin{aligned}
C_p^\circ &= 7{\cdot}219 + 2{\cdot}374 \times 10^{-3}T + 2{\cdot}67 \times 10^{-7}T^2 \\
H^\circ &= -57{\cdot}016 + 7{\cdot}219T + 1{\cdot}187 \times 10^{-3}T^2 + 0{\cdot}89 \times 10^{-7}T^3 \\
S^\circ &= 4{\cdot}08 + 16{\cdot}623 \log T + 2{\cdot}374 \times 10^{-3}T + 1{\cdot}34 \times 10^{-7}T^2
\end{aligned}
$$

[from Spencer and Flanagan (*loc. cit.*), Brickwedde, Moskow, and Aston (*loc. cit.*), Giauque and Archibald (*J. Amer. Chem. Soc.*, 1937, **59**, 56), and Gordon (*J. Chem. Physics*, 1934, **2**, 65)].

Then for ether

$$
\begin{aligned}
C_p^\circ &= 2{\cdot}049 + 97{\cdot}320 \times 10^{-3}T - 342{\cdot}49 \times 10^{-7}T^2 \\
H^\circ &= -36{\cdot}447 - 2{\cdot}043T + 48{\cdot}661 \times 10^{-3}T^2 - 112{\cdot}39 \times 10^{-7}T^3 \\
S^\circ &= 112{\cdot}58 - 4{\cdot}695 \log T + 97{\cdot}33 \times 10^{-3}T - 171{\cdot}1 \times 10^{-7}T^2 - 10{\cdot}020T^{-1} \\
F^\circ &= -36{\cdot}447 - 95{\cdot}05T - 48{\cdot}77 \times 10^{-3}T^2 + 56{\cdot}92 \times 10^{-7}T^3 + 4{\cdot}718T \log T.
\end{aligned}
$$

These results are recorded in the following table, together with values in the literature, extrapolated values being marked with an asterisk.

Thermodynamic values for ethyl ether.

Temp., °K.	285	293	372	400	450	500
C_p° (this work)	—	—	29·4 *[3]	31·4	34·6	37·9
C_p° (spec.)[a]	—	—	30·6	32·3	35·3	38·2
H°	—	−33,149 *[2]	—	−30,196	−28,530	−26,714
S°	92·5 *[1]	—	—	111·6	119·2	124·3

[a] Calc. from spectroscopic functions by Dobratz's method (*Ind. Eng. Chem.*, 1941, **33**, 759).

[1] Parks and Huffman (*J. Amer. Chem. Soc.*, 1924, **46**, 1753) give 88·9.

[2] The heat of combustion recorded by Stohmann, Rodatz, and Herzberg (*J. pr. Chem.*, 1887, **35**, 410) leads to H° −44,935.

[3] Jennings and Bixler (*J. Physical Chem.*, 1934, **38**, 747) give 32·1.

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DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY,
UNIVERSITY OF NATAL, DURBAN, SOUTH AFRICA.

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98. *Optical Activation by Asymmetric Solvent Action.*

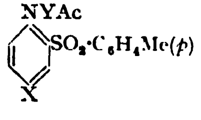
By C. BUCHANAN and S. H. GRAHAM.

Both first- and second-order asymmetric transformations have been observed to occur when potentially optically active, but optically unstable, compounds are dissolved in an optically active solvent. The compounds so obtained have a sufficiently high rotation to allow observations to be made of their rates of racemisation in an inactive solvent and to compare the effect of substituents on the optical stability of closely related compounds.

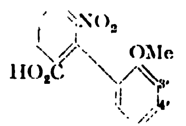
THE existence of a differential solvent effect of an optically active solvent on the two enantiomorphic forms of another active substance was established by Patterson and Buchanan (*J.*, 1940, 290: cf. also Patterson and Lamberton, *J.*, 1937, 1453) who showed that, while the molecular solution volumes of a pair of enantiomorphs were identical when measured in a symmetrical solvent, they differed by a small, but definite, amount when measured in an asymmetric solvent. Several workers have examined the possibility of resolving racemates by means of an asymmetric solvent, *e.g.*, by determining the solubility of the two enantiomorphs separately in an active solvent or by crystallising or extracting the racemate by means of an active solvent. No differentiation of the kind sought was found (Turner and Harris, *Quart. Reviews*, 1948, 327). Turner and Harris (*loc. cit.*) state that " Generally speaking, racemates cannot be even partially resolved by crystallisation from an optically active solvent. This is what might be expected, unless one antipode crystallised with solvent of crystallisation. An example remains to be discovered in which association with an optically active solvent, by hydrogen bonding for example, is responsible for solubility differences in a pair of optical isomerides . . . Some such loose association, with preference for one isomeride, must be responsible for cases of partial resolution by adsorption on optically active adsorbents." The very slight solvent effect observed by Patterson and Buchanan also supports the view that resolution of an optically stable compound is unlikely. We thought, however, that this effect might be made more manifest by examining optically unstable compounds of the type used in asymmetric transformations, *i.e.*, that the asymmetric solvent might influence the relative stabilities and solubilities of these compounds in such a manner as to lead to products showing a measurable rotation. To test this possibility a representative series of optically active but optically unstable compounds was examined in an optically stable solvent.

The asymmetric solvent employed most generally was ethyl (+)-tartrate, which, apart from its ready availability, possessed several advantages. It is a most powerful solvent, a large variety of compounds of most diverse type dissolving in it, including the sodium salts of sulphonic acids. Owing to the fact that it is water-soluble its removal from solid materials after recrystallisation is a matter of extreme ease, while water-soluble compounds can be freed from it by extraction with ether.

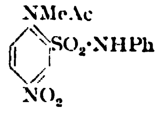
The first compound to be examined extensively was 2-acetomethylamido-5 : 4′-dimethyldiphenyl sulphone (I, X = Y = Me), which owes its asymmetry to restricted rotation about



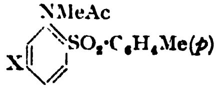
(I.)



(II.)



(III.)



(IV.)

the bond joining nitrogen to the benzene ring. Experiments with this compound are typical of the procedure employed. A supersaturated solution, prepared by warming (I) with ethyl (+)-tartrate, was kept at room temperature till crystallisation appeared to be complete. The resulting crystals were separated as far as possible from the mother-liquor by filtration at the pump, washed with a little alcohol and copiously with water, and dried *in vacuo*. In chloroform solution these crystals gave a dextrorotation ($\alpha \sim +0{\cdot}2°$). The material remaining in the ethyl (+)-tartrate mother-liquors was precipitated by addition of water, washed, and dried: this gave a lævorotation ($\alpha \sim -0{\cdot}15°$) in chloroform solution. Both samples mutarotated to zero rotation, the half-life period at room temperature being 19 minutes.

When a sufficiently dilute solution of the sulphone in ethyl (+)-tartrate was kept at room temperature for a few hours so that no crystallisation occurred, the material in solution was found to be lævorotatory. As this was the whole amount of the originally optically inactive sulphone, a first-order transformation must have occurred, while the activity of the sample obtained by crystallisation was almost certainly due to a second-order transformation. It is of interest that this compound obeys the van't Hoff–Dimroth relationship, which states that the less soluble form of the compound should also be the less stable.

The same sample can be repeatedly activated in this manner and allowed to racemise in chloroform solution, each activation giving substantially the same rotation value, while the sample at the end remains unchanged in melting point. Thus the observed rotations cannot be due to any interaction between the solute and solvent with formation of an optically active impurity derived from the optically active solvent. Moreover, in several of the examples described below the observed rate of racemisation agrees well with that recorded by other workers who activated the substances by formation of diastereoisomeric salts in the normal manner.

With increase in temperature of the solution the activation effect decreases, and, in the case of this sulphone, is negligible at 84°. This temperature effect was observed to apply both to first- and to second-order transformations.

Compound (I) was also examined in other optically active solvents. Ethyl (−)-tartrate, as expected, gave the same results as ethyl (+)-tartrate except for the reversal of the direction of rotation, *i.e.*, the crystals were lævorotatory and the material precipitated from the mother-liquors dextrorotatory. (−)-Menthyl acetate gave a second-order transformation. No transformation was observed, however, when (+)- or (−)-*sec.*-octyl alcohol was used as asymmetric solvent. The solubility of the sulphone in cold *sec.*-octyl alcohol is low and crystallisation took place rapidly; crystallisation of the sulphone from ethyl tartrate took several days. However, crystallisation of the sulphone from menthyl acetate was also rapid, so it is difficult to say whether rate of crystallisation is an important factor.

The related *N*-ethyl compound (I; X = Me, Y = Et) has also been found to undergo both first- and second-order transformations in ethyl (+)-tartrate. As expected, it was found to be optically much more stable than the *N*-methyl compound, having a half-life period of about 6 hours as against 19 minutes. This is of interest as showing that a compound of such relatively high optical stability is capable of undergoing asymmetric transformations in an asymmetric solvent.

Another closely related compound, sodium *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonate, was found to undergo a first-order transformation in ethyl (+)-tartrate and a second-order transformation in (+)-*sec.*-butyl alcohol. The half-life period of racemisation was 150 minutes at 18°; Mills and Kelham (*J.*, 1937, 274) give 175 minutes at 16·6° and 70 minutes at 25°.

These results show that optical activation can be achieved by asymmetric solvent action. Moreover, this method can be applied to compounds which lack a salt-forming group and so cannot be resolved by the normal means. The compounds obtained, although not optically pure, have a sufficiently high rotatory power to allow observations to be made of their rates of racemisation and thus to compare the optical stabilities of related compounds. It was decided to study a series of related sulphones and similar compounds in this way, in the hope that an example exhibiting a more complete activation effect might be obtained.

It has been shown by Adams and his school that, in the case of optically active diphenyl derivatives, substituents other than those actually involved in the steric interference can influence the optical stability of the compound (Adams *et al.*, *J. Amer. Chem. Soc.*, 1932, **54**, 2966, 4434; 1934, **56**, 1787; 1935, **57**, 1592). Adams investigated the series of compounds obtained when a substituent X is introduced into positions 3′, 4′, or 5′ of the diphenyl molecule (II). He found that for each of the three series of compounds the optical stability increases in the order $H < OCH_3 < CH_3 < Cl < Br < NO_2$. A similar investigation was carried out on the sulphone type of molecule. The substituents Cl, Br, OCH_3 were successively introduced in place of the *p*-methyl group (I; X = Cl, Br, OCH_3; Y = Me or Et); the *N*-methyl-*p*-bromo-compound, however, was not prepared in sufficient quantity for experiments with ethyl (+)-tartrate. Of these compounds, all underwent first-order transformations in ethyl (+)-tartrate and, with the single exception of the *N*-ethyl-*p*-chloro-compound, all underwent second-order transformations also. The relative optical stabilities are shown in Table I. Since the observed rotations are small, these values are only approximate, but they allow the various compounds to be arranged in order of optical stability, which decreases in the order $OCH_3 > CH_3 > Cl > Br$. It will be observed that the substituents fall into the same sequence as that observed by Adams but that the order is reversed.

TABLE I.

Half-life periods of racemisation of sulphones (I).

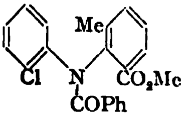
X =	Y = CH_3.	Y = C_2H_5.	X =	Y = CH_3.	Y = C_2H_5.
p-Br	—	30 mins.	*p*-CH_3	19 mins.	720 mins.
p-Cl	3 mins.	120 mins.	*p*-OCH_3	41 mins.	many hours

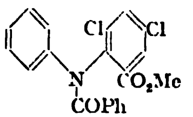
It was desired also to investigate the nitro-substituted sulphone (I; X = NO_2), but no route leading conveniently to its synthesis could be found. The closely related sulphonanilide (III) was not activated by ethyl (+)-tartrate, nor did 5-nitro-2-acetomethylamidobenzenesulphonic acid give any evidence of asymmetric transformation with brucine or quinidine. In so far as conclusions may be drawn from such negative results, it seems that a nitro-group *para* to the methylamido-group destroys the asymmetry of the molecule, possibly because of resonance involving both the nitro- and the amido-group.

The unsubstituted and *m*-substituted compounds (IV; X = H, Br, Cl, CH_3, OCH_3) could not be activated by solution in ethyl (+)-tartrate. These observations were most surprising, having regard to the very consistent results obtained with the *p*-substituted sulphones. The explanation possibly lies in the difference in physical properties. The unsubstituted and *m*-substituted sulphones are much more soluble in common solvents than the *p*-compounds and display a greater tendency to form supersaturated solutions, the most extreme case being that of the *m*-chloro-compound, solutions of which in acetic acid remained supersaturated for up to two days, crystallising rapidly on the addition of a crystal of the sulphone. With one exception they did not crystallise from ethyl (+)-tartrate and had to be precipitated by water, the solute separating first as an oil which solidified on more or less prolonged standing. The *m*-nitro-compound (IV; X = NO_2), which did not display this tendency to form supersaturated solutions, was crystallised from ethyl (+)-tartrate but it gave no evidence of activation.

Derivatives of Benzodiphenylamide.—Three *o*-substituted benzodiphenylamides (V, VI, VII), compounds of low optical stability similar to compounds investigated by Turner and his school, have been examined. The acids corresponding to the first two of these esters have been resolved by Jamison and Turner (*J.*, 1940, 264), who measured their rates of racemisation;

both esters were observed to undergo both first- and second-order transformations in ethyl (+)-tartrate. The rotation of the product of the first-order transformation of (V) was the largest observed in the course of this work ($[\alpha]_{5461} = -4{\cdot}4°$). In this case the enantiomorph which is present in excess in solution also predominates in the crystals which separate out, which have $[\alpha]_{5461} = -0{\cdot}75°$. Crystallisation from ethyl (−)-tartrate gave a product having $[\alpha]_{5461} = +0{\cdot}79°$. The observed rates of racemisation (Table II) of these esters corresponded fairly satisfactorily with those recorded by Turner for the acids.


(V.)


(VI.)

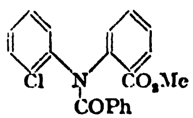

(VII.)

TABLE II.

	Half-life period, mins.		Half-life period, mins.
Acid (V)	10·5	Ester (V)	8
Acid (VI)	4·6	Ester (VI)	5

The third ester (VII) was observed to undergo a first- but not a second-order transformation. The crystals which separated from ethyl (+)-tartrate were optically inactive, but the material precipitated from the mother-liquors was lævorotatory. It is difficult to say why this compound should not have undergone a second-order transformation. It had been observed that, in the case of 2-acetomethylamido-5 : 4′-dimethyldiphenyl sulphone, any vigorous agitation of the ethyl (+)-tartrate solution while filtering the crystals, or any scratching or the walls of the containing vessel, caused precipitation of lævorotatory material from the mother-liquors along with the dextrorotatory crystals, thus obscuring the rotation of the material actually produced by crystallisation. It is possible that in this case also some form of coprecipitation obscures the effect of a possible second-order transformation. The half-life period of this compound was large compared with that of (VI) (15 mins. as against 5 mins.). This is not very surprising having regard to the observations made on the effect of substituents on the optical stability of the sulphones, and to similar observations in the diphenyl series recorded by Kuhn and Albrecht (*Annalen*, 1927, **458**, 221).

Prototropic Compounds.—A compound which exists in solution as an equilibrium mixture of two tautomers, one of which is asymmetric and the other symmetric, should be capable of undergoing asymmetric transformations. Only a few instances of this are recorded in the literature, and most of the compounds in question were unsuitable for the purposes of the present work. Leuchs and Wutke (*Ber.*, 1913, **46**, 2420; 1921, **54**, 1830) investigated two compounds of this type, 2-*o*-carboxybenzylindan-1-one and hydrocarbostyril-3-carboxylic acid. Of these, the first is difficult to prepare and the second sparingly soluble, so that only dilute solutions of the compound would be available for polarimetric examination and the slight activation to be expected by the use of an asymmetric solvent might be overlooked. More recently, Davidson and Turner (*J.*, 1945, **843**) have shown that compounds of the malonoanilic acid type undergo asymmetric transformations with optically active bases.

One of these compounds, benzylmalono-*o*-toluidic acid, was prepared and recrystallised from ethyl (+)-tartrate. The material which crystallised was lævorotatory; no mutarotation occurred in alcoholic solution but the rotation disappeared on addition of alcoholic alkali. These observations are in accord with Turner's findings. No polarimetric measurements could be made on the material recovered from the ethyl tartrate mother-liquors owing to the presence of highly coloured impurities.

On the basis of Leuchs and Wutke's observations on the substituted indanone it seemed possible that the hydrogen atom attached to a carbon atom adjacent to a single carbonyl group might be sufficiently mobile to permit of asymmetric transformations. An α-alkyldeoxybenzoin was thought to be a suitable compound for experiment, and the α-benzyl compound was accordingly prepared. α-Benzyldeoxybenzoin, however, apparently reacted with ethyl (+)-tartrate to give a highly active product, which we were unable to isolate in a pure state and did not examine further. The related compound, *α-benzyldeoxybenzoin-2-carboxylic acid*, was resolved in the usual manner. This acid formed a brucine salt from which, after four crystallisations from ethyl acetate, the (−)-base, (+)-acid was isolated, $[\alpha]_{5461} = -12{\cdot}1°$. On treatment with hydrochloric acid, the (+)-acid was produced, $[\alpha]_{5461} = +27{\cdot}5°$. This acid did not racemise in chloroform solution, as did that of Leuchs and Wutke. It racemised slowly, however, on crystallising from hot acetic acid; it also racemised in hot aqueous-alcoholic alkali. Esterification of the active acid with diazomethane produced the (+)-*methyl* ester, $[\alpha]_{5461} = +29{\cdot}3°$. This ester was heated under reflux in methanolic solution for 48 hours; the recovered ester had $[\alpha]_{5461} = +31{\cdot}8°$, showing that no racemisation had taken place in the process. The increase in rotation of the ester was presumed to be due to some purification that had taken place in the course of the attempted racemisation. This result is rather difficult to reconcile with Leuchs and Wutke's claims, but it indicates that α-benzyldeoxybenzoin itself would be unlikely to undergo an asymmetric transformation.

Optically inactive methyl α-benzyldeoxybenzoin-2-carboxylate was crystallised from ethyl (+)-tartrate solution. Almost all the ester separated from the solution: the crystals showed no rotation.

αα′-Dinitrodibenzyl, which contains the nitro–*aci*nitro-system, was also investigated. This substance has been shown to exist in two isomeric forms, one m. p. 235° and the other m. p. 152° (Schmidt, *Ber.*, 1901, **34**, 3540; Brown and Shriner, *J. Org. Chem.*, 1937—1938, **2**, 376). The compound contains two asymmetric carbon atoms; one of the isomers will be the racemic and the other the *mesó*-form of the compound. No means of distinguishing them exists, since, as they lack any salt-forming group, no method of resolution, other than asymmetric solvent action, is applicable. It was hoped that the racemic form might undergo an asymmetric transformation in ethyl (+)-tartrate solution, and there was a possibility that the *meso*-form might undergo partial conversion into its isomer under the influence of the ethyl (+)-tartrate.

The higher-melting isomer crystallised rapidly from the ethyl tartrate. In the first experiment the crystals were found to be lævorotatory in nitrobenzene solution; mutarotation occurred at room temperature. A certain amount of decomposition of the dinitrodibenzyl had taken place, however, as indicated by the evolution of nitrous fumes; it had been necessary to heat the dinitrodibenzyl and the ethyl tartrate for rather a long time near the boiling point of the ethyl tartrate to bring the sparingly soluble nitro-compound into solution. The experiment was repeated, care being taken to avoid any decomposition of the nitro-compound; the crystals which separated were optically inactive. No rotation was detected in the crystals when the first crystals were allowed to separate at 86° (to permit of slow crystallisation). The rotation observed in the first instance was possibly due to chance preferential inoculation of the solution or to an asymetric decomposition. All these samples melted at 235°; there was no indication of any conversion into the lower-melting isomer. When the other isomer was crystallised from ethyl (+)-tartrate there was no indication of any asymmetric transformation or of any conversion into the higher-melting isomer.

EXPERIMENTAL.

(All polarimeter readings were made in a 2-dm. tube with mercury green light, λ = 5461 A.; all m. p.s are uncorrected.)

5-Substituted 2-Acetoalkylamido-4′-methyldiphenyl Sulphones.—The toluene-*p*-sulphonyl derivatives of *p*-methyl-, *p*-methoxy-, *p*-chloro-, and *p*-bromo-*N*-methyl- and *N*-ethyl-aniline were all prepared by normal methods. Rearrangement to the *o*-amino-sulphone was carried out by heating it at 100° with an equal weight of 96% sulphuric acid for 2 hours; when the mixture was cooled and poured into water the sulphones were precipitated. The following 2-amino-4′-methyldiphenyl sulphones were obtained: *N*-acetyl-*N*:5-dimethyl-, prisms, m. p. 168° (lit., 138°; Halberkaan, *Ber.*, 1921, **54**, 1835) (Found: C, 64·5; H, 5·8. Calc. for $C_{17}H_{19}O_3NS$: C, 64·4; H, 6·0%); *N*-acetyl-5-methyl-*N*-ethyl-, needles (alcohol), m. p. 145°; *N*-acetyl-5-methoxy-*N*-methyl-, prisms (alcohol), m. p. 138°; *5-methoxy*-N-*ethyl-*, prisms (alcohol), m. p. 94° (Found: C, 63·1; H, 6·3; N, 4·8. $C_{16}H_{19}O_3NS$ requires C, 63·0; H, 6·2; N, 4·6%); N-*acetyl-5-methoxy*-N-*ethyl-*, prisms (alcohol), m. p. 145° (Found: C, 62·6; H, 6·1; N, 4·3. $C_{18}H_{21}O_4NS$ requires C, 62·2; H, 6·0; N, 4·0%); *5-chloro*-N-*methyl-*, needles (alcohol), m. p. 155° (Found: C, 57·1; H, 4·8; N, 5·1. $C_{14}H_{14}O_2NClS$ requires C, 56·9; H, 4·7; N, 4·7%); *5-chloro*-N-*acetyl*-N-*methyl-*, needles (alcohol), m. p. 159° (Found: C, 57·0; H, 4·7; N, 4·4. $C_{16}H_{16}O_3NClS$ requires C, 56·9; H, 4·7; N, 4·2%); *5-chloro*-N-*ethyl-*, needles (alcohol), m. p. 136° (Found: C, 58·1; H, 5·1; N, 4·8. $C_{15}H_{16}O_2NClS$ requires C, 58·2; H, 5·2; N, 4·5%); *5-chloro*-N-*acetyl*-N-*ethyl-*, plates (alcohol), m. p. 153° (Found: C, 58·0; H, 5·4; N, 3·7. $C_{17}H_{18}O_3NClS$ requires C, 58·0; H, 5·2; N, 4·0%); *5-bromo*-N-*methyl-*, needles (alcohol), m. p. 161° (Found: C, 50·0; H, 4·3. $C_{14}H_{14}O_2NBrS$ requires C, 49·7; H, 4·2%); *5-bromo*-N-*acetyl*-N-*methyl-*, needles (alcohol), m. p. 173° (Found: C, 50·1; H, 4·3. $C_{16}H_{16}O_3NBrS$ requires C, 50·3; H, 4·2%); *5-bromo*-N-*ethyl-*, needles (alcohol), m. p. 141° (Found: C, 50·9; H, 4·8. $C_{15}H_{16}O_2NBrS$ requires C, 50·9; H, 4·6%); *5-bromo*-N-*acetyl*-N-*ethyl-*, needles (alcohol), m. p. 144° (Found: C, 51·5; H, 4·6. $C_{17}H_{18}O_3NBrS$ requires C, 51·6; H, 4·6%).

2-Acetomethylamido-5:4′-dimethyldiphenyl Sulphone in Ethyl (+)-Tartrate.—(*a*) The sulphone (3 g.) was dissolved in ethyl (+)-tartrate (10 c.c.). After 5 hours at room temperature the sulphone was precipitated by addition of water, filtered off, washed thoroughly with water, and dried *in vacuo*; 1·336 g. in chloroform (15 c.c.) had α^{18} −0·20°, rising to zero, half-life period = 19 minutes.

(*b*) The sulphone (5 g.) was crystallised from ethyl (+)-tartrate (7 c.c.). When crystallisation appeared to be complete, the crystals were carefully drained as free from ethyl tartrate as possible, washed with a little alcohol, then washed thoroughly with water, and dried *in vacuo*. It was essential not to scratch or in any way agitate the crystals while they were still in contact with ethyl tartrate, as this caused precipitation of lævorotatory material from the mother-liquors. The material remaining in the mother-liquors was precipitated and treated as in (*a*) above. Crystals: 2·034 g. in 15 c.c. of chloroform had α^{17} +0·17°, falling to zero, half-life period = 19 minutes. Precipitate: 1·271 g. in 15 c.c. of chloroform had α^{16} −0·15°, half-life period of mutarotation = 19 minutes.

Effect of increase of temperature. The sulphone (5 g.) was crystallised from ethyl (+)-tartrate (7 c.c.) at 84°, and samples were kept in the ester solution at 42° and 84° for several hours without crystallisation taking place; the several fractions were then recovered in the appropriate manner. The samples treated at 84° possessed negligible rotations (*ca.* ±0·01° for 10% solutions in chloroform). The 42° sample had $[\alpha]^{17}$ −0·5° (*c*, 12 in chloroform).

2-Acetomethylamido-5 : 4′-dimethyldiphenyl Sulphone in Other Asymmetric Solvents.—(a) *Ethyl* (−)-*tartrate.* The sulphone (3 g.) was recrystallised from ethyl (−)-tartrate (5 c.c.). Crystals: 0·438 g. in 15 c.c. of chloroform had α^{20} −0·05°, rising to zero in 1 hour. Precipitate: 1·6446 g. in 15 c.c. of chloroform had α^{19} +0·13° falling to zero in 2 hours.

(b) (−)-*Menthyl acetate.* A solution of 3 g. in 20 c.c. was allowed to crystallise completely; the crystals were filtered off and washed with cold methanol: 1·03 g. in 15 c.c. of chloroform had α^{20} +0·08°, falling to −0·10° in 80 minutes, the final lævorotation being presumably due to the presence of residual menthyl acetate.

(c) (+)- *and* (−)-sec.-*Octyl alcohol.* Solutions of 3 g. of the sulphone in 10 c.c. each of the alcohols were allowed to crystallise; the crystals, representing almost the whole of the solute, were in both cases optically inactive.

2-Acetoethylamido-5 : 4′-dimethyldiphenyl Sulphone in Ethyl (+)-*Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). Crystals: 1·8164 g. in 15 c.c. of chloroform had α^{22} +0·11°, falling to zero, half-life period *ca.* 6 hours. Precipitate: 1·254 g. in 15 c.c. of chloroform had α^{20} −0·08°, rising to zero.

A solution of 1 g. in 10 c.c. of ethyl (+)-tartrate was kept for a few days, and the solute recovered by precipitation with water; 1·5177 g. in 15 c.c. of chloroform had α^{20} −0·08°, rising to zero.

Other Compounds of Type (I) *in Ethyl* (+)-*Tartrate.*—The compounds were in turn crystallised from ethyl (+)-tartrate (3 g. in 5—10 c.c.), giving two fractions, crystals, A, and precipitate from the mother-liquors, B. Samples (1 g.) of the sulphones were also kept in solution in ethyl (+)-tartrate (10 c.c.) for some hours and then the solute was recovered by precipitation with water to give fraction C. The observed rotations for the various fractions in chloroform solution (15 c.c.) of all these compounds are tabulated below.

Sodium N-*Acetyl*-N-*methyl*-p-*toluidine-3-sulphonate in Asymmetric Solvents.*—*N*-Methyl-*p*-toluidine was prepared by the method of Halberkaan (*loc. cit.*), and its acetyl derivative sulphonated and acetylated by the method of Mills and Kelham (*loc. cit.*). The hydrated salt melted at 84°.

(a) *Ethyl* (+)-*tartrate.* A solution of the salt (2 g.) in ethyl tartrate (5 c.c.) was kept at room temperature for 5 hours, and the solute recovered by precipitation with moist ether (use of dry ether led to difficulty in obtaining a solid precipitate). The salt was freed from ethyl tartrate by extraction with ether in a Soxhlet apparatus: 1·267 g. in 15 c.c. of water had α^{18} −0·08°, rising to zero, half-life period 150 minutes.

(b) (+)-sec.-*Butyl alcohol.* The salt (2 g.) was recrystallised from moist (+)-*sec.*-butyl alcohol (7·5 c.c.). The crystals were filtered off at the pump and washed with ether several times: 1·562 g. in 15 c.c. of water had α^{18} −0·07°, rising to zero in about 5 hours.

5-Nitro-2-methylaminobenzenesulphonanilide.—2-Chloro-5-nitrobenzenesulphonanilide was boiled for 48 hours in methanolic solution with an excess of methylamine carbonate; the *methylamino*-compound formed needles, m. p. 169°, from alcohol (Found: C, 51·0; H, 4·4; N, 13·8. $C_{13}H_{13}O_4N_3S$ requires C, 50·7; H, 4·2; N, 13·7%); its *acetyl* derivative (III) formed prisms, m. p. 222°, from dioxan (Found: C, 51·8; H, 4·4; N, 12·2. $C_{15}H_{15}O_5N_3S$ requires C, 51·6; H, 4·4; N, 12·0%). Crystallisation from ethyl (+)-tartrate gave an inactive product (*c*, 10 in dioxan).

Substituents.		A.		B.		C.		Half-life period.
		Initial *a*.	Wt., g.	Initial *a*.	Wt., g.	Initial *a*.	Wt., g.	
X = OMe	Y = Me ...	−0·10°	0·432	−0·11°	0·962	−0·08°	0·746	41 mins.
	Y = Et ...	+0·03	0·494	−0·10	1·065	—	—	very large
X = Cl	Y = Me ...	−0·20	1·078	−0·10	0·975	−0·04	0·955	3 mins.
	Y = Et ...	nil	0·958	+0·14	0·756	+0·16	0·937	120 mins.
X = Br	Y = Et ...	−0·13	0·720	+0·12	0·750	—	—	30 mins.

Sodium 5-Nitro-2-methylaminobenzenesulphonate.—Dry *p*-nitro-*N*-acetyl-*N*-methylaniline (21·6 g.) was sulphonated with chlorosulphonic acid (13 g.) at 120—135° for 4 hours with stirring. The product was dissolved in water, neutralised with sodium carbonate, and evaporated to dryness. Crystallisation from 90% aqueous alcohol gave the hydrated *salt* as yellow needles (Found: C, 30·0; H, 3·8. $C_7H_7O_5N_2SNa,1{\cdot}5H_2O$ requires C, 29·9; H, 3·6%). Acetylation gave the N-*acetyl* derivative, the hydrated salt being dehydrated at 100° (Found: C, 36·3; H, 3·2; N, 9·5. $C_9H_9O_6N_2SNa$ requires C, 36·5; H, 3·0; N, 9·5%).

(−)-*Brucine 5-Nitro-2-acetomethylamidobenzenesulphonate.*—The sodium salt (1·5 g.) in water (4 c.c.) was treated with a solution of brucine (2·3 g.) in water (10 c.c.) containing acetic acid (0·41 g.). The solution became deep red and on storage the *brucine* salt separated (Found: C, 57·4; H, 5·5; N, 8·4. $C_{32}H_{36}O_{10}N_4S$ requires C, 57·5; H, 5·1; N, 8·4%). The salt was recrystallised from water, alcohol, in which it was sparingly soluble, and nitrobenzene (readily soluble). The rotation in each case was

0·0° (*c*, 10 in chloroform). No change in rotation occurred on further recrystallisation from water; no mutarotation was observed. A saturated solution of the brucine salt in chloroform was treated with the theoretical quantity of alcoholic sodium ethoxide at 0°. The precipitated sodium salt was optically inactive. The zero value for the rotation of the brucine salt may be due to optical activation of the acid so that its rotation exactly counterbalances that of the brucine; but, in the absence of mutarotation or optical activity in the recovered acid, no definite conclusion can be drawn from anomalous rotation (cf. Kharasch *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 1646).

(+)-*Quinidine 5-Nitro-2-acetomethylamidobenzenesulphonate.*—The sodium salt (8·88 g.) in water (35 c.c.) was treated with quinidine (9·72 g.) in water (25 c.c.) containing acetic acid (1·8 g.). The precipitated yellow viscous oil slowly crystallised to pale yellow prisms of the quinidine salt (10 g.). The rotation ($[\alpha]^{20}$ +210·5°) was not raised by repeated crystallisation from ethyl acetate; no mutarotation was observed. Extraction of a chloroform solution of the salt with dilute ammonia solution gave an optically inactive solution of the ammonium salt.

4-*Substituted 2-Acetomethylamido-4′-methyldiphenyl Sulphones.*—The appropriate *o*-nitroaryl halides were condensed with sodium *p*-tolylsulphide, the thio-ethers were oxidised (hydrogen peroxide in acetic acid) to sulphones, and the nitro-groups then reduced to amino-groups with stannous chloride in aqueous-alcoholic hydrochloric acid. Acetylation of the amino-sulphones, followed by methylation with methyl sulphate and alcoholic sodium ethoxide, gave the required compounds. The following substituted 4′-methyldiphenyl sulphides have not previously been described: 2-*nitro-4-methoxy-*, orange prisms (from methanol), m. p. 96° (Found: C, 61·3; H, 4·6. $C_{14}H_{13}O_3NS$ requires C, 61·1; H, 4·8%); 4-*bromo-2-nitro-*, elongated orange prisms (from dioxan), m. p. 124° (Found: C, 48·6; H, 3·3. $C_{13}H_{10}O_2NBrS$ requires C, 48·2; H, 3·1%). The following substituted 4′-methyldiphenyl sulphones are also new: 2-*acetomethylamido-*, prisms (from alcohol), m. p. 121° (Found: C, 63·5; H, 5·0. $C_{16}H_{17}O_3NS$ requires C, 63·4; H, 5·3%); 2-*acetomethylamido-4-methyl-*, needles (from alcohol), m. p. 161° (Found: C, 64·5; H, 5·7; N, 4·5. $C_{17}H_{19}O_3NS$ requires C, 64·4; H, 6·0; N, 4·5%); 2-*nitro-4-methoxy-*, needles (from alcohol), m. p. 127° (Found: C, 54·8; H, 4·2. $C_{14}H_{13}O_5NS$ requires C, 54·8; H, 4·2%); 2-*amino-4-methoxy-*, small needles (from benzene), m. p. 153° (Found: C, 60·7; H, 5·5. $C_{14}H_{15}O_3NS$ requires C, 60·7; H, 5·4%); 2-acetamido-4-methoxy-, needles (from alcohol), m. p. 115°; 2-*acetomethylamido-4-methoxy-*, prisms (from methanol), m. p. 147° (Found: C, 61·3; H, 5·8; N, 4·4. $C_{17}H_{19}O_4NS$ requires C, 61·3; H, 5·7; N, 4·2%); 4-*chloro-2-amino-*, white platelets (from alcohol), m. p. 137° (Found: C, 55·6; H, 4·3. $C_{13}H_{12}O_2NClS$ requires C, 55·4; H, 4·3%); 4-*chloro-2-acetamido-*, needles (from methanol), m. p. 129° (Found: C, 55·8; H, 4·3. $C_{15}H_{14}O_3NClS$ requires C, 55·7; H, 4·3%); 4-*chloro-2-acetomethylamido-*, prisms (from acetic acid), m. p. 175° (Found: C, 57·1; H, 4·6; N, 4·3. $C_{16}H_{16}O_3NClS$ requires C, 56·9; H, 4·8; N, 4·2%); 4-*bromo-2-nitro-*, white needles (from alcohol), m. p. 132° (Found: C, 43·9; H, 2·9. $C_{13}H_{10}O_4NBrS$ requires C, 43·8; H, 2·8%); 4-*bromo-2-amino-*, prisms (from alcohol), m. p. 154° (Found: C, 47·7; H, 3·8. $C_{13}H_{12}O_2NBrS$ requires C, 47·9; H, 3·7%); 4-*bromo-2-acetamido-*, white prisms (from methanol), m. p. 132° (Found: C, 49·0; H, 4·1. $C_{15}H_{14}O_3NBrS$ requires C, 49·0; H, 3·8%); 4-*bromo-2-acetomethylamido-*, white prisms (from alcohol), m. p. 160° (Found: C, 50·2; H, 4·2; N, 4·0. $C_{16}H_{16}O_3NBrS$ requires C, 50·3; H, 4·2; N, 3·7%).

4-*Substituted 2-Acetomethylamido-4′-methyldiphenyl Sulphones in Ethyl* (+)-*Tartrate.*—Solutions of the compounds (2 g.) in the ester (15 c.c.) were kept at room temperature for several hours, and the solute then recovered by precipitation with water. In each case the recovered material was optically inactive. The unsubstituted sulphone (IV; X = H) (2 g.) was crystallised from ethyl (+)-tartrate (5 c.c.). Both the crystals which separated and the material remaining in the mother-liquors were optically inactive in chloroform solution.

4-*Nitro-2-acetomethylamido-4′-methyldiphenyl Sulphide.*—2-Chloro-5-nitro-*N*-methylacetanilide was condensed with sodium *p*-tolyl sulphide; the *sulphide* formed dull yellow prisms, m. p. 157° from alcohol, (Found: C, 60·8; H, 5·1. $C_{16}H_{16}O_3N_2S$ requires C, 60·8; H, 5·1%). Oxidation with hydrogen peroxide in acetic acid gave the *sulphone*, white platelets (from alcohol), m. p. 171° (Found: C, 55·3; H, 4·6. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6%). The latter compound was crystallised from ethyl (+)-tartrate; both the crystals and the material recovered from the mother-liquors were optically inactive.

*Methyl 2-Chloro-*N*-benzoyl-6′-methyldiphenylamine-2′-carboxylate* (prisms, m. p. 169°) *in Asymmetric Solvents.*—(a) *Ethyl* (+)-*tartrate.* The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). Crystals: 1·1022 g. in 15 c.c. of chloroform had α^{20} −0·11°, rising to zero, half-life period = 8 minutes. Precipitate: 0·4623 g. in 15 c.c. of chloroform had α^{20} −0·27°, rising to zero, half-life period = 8 minutes. A solution of the compound (2 g.) in ethyl (+)-tartrate (30 c.c.) was kept for several hours, and the solute precipitated by addition of water; 1·0899 g. in 15 c.c. of chloroform had α^{22} −0·32°, rising to zero, half-life period = 8 minutes.

(b) *Ethyl* (−)-*tartrate.* The compound (3 g.) was recrystallised from ethyl (−)-tartrate (8 c.c.). Crystals: 1·322 g. in 15 c.c. of chloroform had α^{21} +0·14°, falling to zero in 30 minutes. Precipitate: insufficient for examination.

*Methyl 4 : 6-Dichloro-*N*-benzoyldiphenylamine-2-carboxylate* (prisms, m. p. 119°) in *Ethyl* (+)-*Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (9 c.c.). Crystals: 20·25 g. in 15 c.c. of chloroform had α^{19} −0·09°, rising to zero, half-life period = 5 minutes. Precipitate: 0·57 g. in 15 c.c. of chloroform had α^{19} −0·03°, rising to zero. A solution of the compound (2 g.) in ethyl (+)-tartrate (20 c.c.) was kept for 24 hours, and the solute precipitated with water; 1·55 g. in 15 c.c. of chloroform had α^{20} −0·11°, rising to zero.

N-o-*Chlorophenylbenzimino* o-*carbomethoxyphenyl ether* prisms (from methanol), m. p. 89° (Found: C, 68·6; H, 4·4. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4%), and *methyl 2-chloro-*N*-benzoyldiphenylamine-2′-carboxylate*, prisms, m. p. 123° (Found: C, 68·9; H, 4·5. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4%), were prepared.

*Methyl 2-Chloro-*N*-benzoyldiphenylamine-2′-carboxylate in Ethyl* (+)-*Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). The crystals were optically inactive. Precipitate: 1·653 g. in 15 c.c. of chloroform had α^{17} −0·13°, rising to zero, half-life period = 15 minutes.

A solution of the compound (1 g.) in ethyl (+)-tartrate (5 c.c.) was kept for several hours, and the solute precipitated : 0·955 g. in 15 c.c. of chloroform had α^{19} −0·10°, rising to zero.

Crystallisation of α-Benzyldeoxybenzoin from Ethyl (+)-Tartrate.—α-Benzyldeoxybenzoin (30 g.) was crystallised from ethyl (+)-tartrate (170 c.c.) to give crystals, $[\alpha]^{20}$ −2·11° (*c*, 5 in chloroform), which were then crystallised from more tartrate (200 c.c.) and then successively from four 50-c.c. portions; the succeeding fractions had $[\alpha]^{20}$ −2·3°, −3·8°, −5·2°, −5·7°, −5·7°, −5·7°. The α-benzyldeoxybenzoin recovered from the mother-liquors of the first three crystallisations was combined and crystallised from ethyl (+)-tartrate (30 c.c.) to give crystals (5·8 g.), $[\alpha]^{20}$ +5·7° (*c*, 5 in chloroform), and a precipitate from the mother-liquors (0·3 g.), $[\alpha]^{19}$ +17° (*c*, 2 in chloroform). In a parallel experiment with a different sample of ethyl (+)-tartrate a less soluble fraction was obtained, having $[\alpha]^{21}$ −20°; the soluble fraction had $[\alpha]^{21}$ +20°. The sample, $[\alpha]^{19}$ +17° (0·5 g.), was recrystallised from alcohol (20 c.c.); the crystals (0·3 g.) had $[\alpha]^{20}$ +5·8°, and the material recovered from the mother-liquors had $[\alpha]^{20}$ +30·9°. Similarly, the lævorotatory material of $[\alpha]^{21}$ −20° gave crystals of $[\alpha]^{20}$ −14° and a precipitate from the mother-liquors of $[\alpha]^{20}$ −34°. Owing to the small amount of material available it was not possible to carry this separation further. An attempt at separation by chromatographic analysis of a benzene solution of the active material on a column of activated alumina was unsuccessful.

Benzyl α-Benzyldeoxybenzoin-2-carboxylate.—Methyl deoxybenzoin-2-carboxylate (32 g.) was dissolved in methanol (60 c.c.) containing sodium (5·1 g.) and alkylated with benzyl chloride (29 g., 2 mols.). The *benzyl* ester formed large white needles, m. p. 75° (Found : C, 83·1; H, 5·6. $C_{29}H_{24}O_3$ requires C, 82·9; H, 5·7%). Hydrolysis gave the *acid*, white prisms (from acetic acid), m. p. 171° (Found : C, 79·7; H, 5·4. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5%).

Brucine (+)-α-Benzyldeoxybenzoin-2-carboxylate.—Brucine (16·8 g.) and the foregoing acid (11·3 g.) were dissolved in ethyl acetate (80 c.c.); the crystals which separated on cooling had $[\alpha]^{20}$ −15·3° (*c*, 5 in chloroform). Three crystallisations from ethyl acetate (200 c.c.) gave 7 g. of salt with $[\alpha]^{20}$ −12·1°.

(+)-α-Benzyldeoxybenzoin-2-carboxylic acid obtained by decomposition of the brucine salt with dilute hydrochloric acid had $[\alpha]^{20}$ +27·5 (*c*, 5 in chloroform). The *methyl* ester, obtained by esterification with excess of diazomethane, had $[\alpha]^{20}$ +29·3° (*c*, 4 in methanol), and, after 48 hours' refluxing in methanol, $[\alpha]^{20}$ +31·8° (*c*, 3 in methanol). The ester formed prisms, m. p. 110° (Found : C, 80·0; H, 5·7. $C_{23}H_{20}O_3$ requires C, 80·3; H, 5·8%).

Racemisation of (+)-α-Benzyldeoxybenzoin-2-carboxylic Acid.—A sample of the acid, $[\alpha]^{20}$ +4·85°, was heated at 100° for 33 hours with excess of aqueous-alcoholic sodium ethoxide; it was then optically inactive (*c*, 2 in chloroform). On crystallisation of some of the same sample of acid from acetic acid the crystals were found to be optically inactive (*c*, 2 in chloroform).

Methyl α-Benzyldeoxybenzoin-2-carboxylate in Ethyl (+)-Tartrate.—On crystallisation of the ester (4·7 g.) from ethyl (+)-tartrate (9 c.c.) both the crystals and the precipitate from the mother-liquors were optically inactive (*c*, 8 in chloroform).

αα'-Dinitrodibenzyl.—This was prepared by Schmidt's method (*Ber.*, 1901, **34**, 3540). From 30 g. of stilbene were obtained 12 g. of the higher-melting isomer, m. p. 235°, and 7 g. of the lower-melting isomer, m. p. 142—146°.

αα'-Dinitrodibenzyl in Ethyl (+)-Tartrate.—(a) *High-melting isomer.* This compound (3 g.) was recrystallised from ethyl (+)-tartrate (45 c.c.), some nitrogen dioxide being evolved. Crystals : 0·9467 g. in 15 c.c. of nitrobenzene had α^{20} −0·28°, rising to zero in an hour. When this experiment was repeated with 3 g. of the solute in 60 c.c. of ester, care being taken to avoid decomposition, no optical activity was detected in the crystals even when crystallisation was slow (solution kept in a bath of water slowly cooled from 84° to room temperature).

(b) *Low-melting isomer.* The compound (2 g.) was recrystallised from ethyl (+)-tartrate (10 c.c.) below 140° (conversion into the other isomer takes place above 152°); both the crystals and the material recovered from the mother-liquors were optically inactive and melted at 147°.

We wish to thank Mr. J. M. L. Cameron and Miss R. H. Kennaway who carried out the microanalyses, also the Department of Scientific and Industrial Research for a maintenance grant to one of us (S. H. G.), during the tenure of which part of this work was carried out.

UNIVERSITY OF GLASGOW. [*Received, September 21st, 1949.*]

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99. *The Reaction between Amines and 1-Chloro-2 : 4-dinitrobenzene.*

By O. L. BRADY and F. R. CROPPER.

The reaction of a number of alkylamines and dialkylamines with chlorodinitrobenzene has been studied kinetically, and it has been found that there is a remarkable difference between the rate constants for different amines which is not directly related to their basic strength; for example, the rate constant for dimethylamine is more than 30,000 times that for di*iso*propylamine though the latter is the stronger base.

Evidence is adduced that a steric effect plays an important part in determining the rate constant.

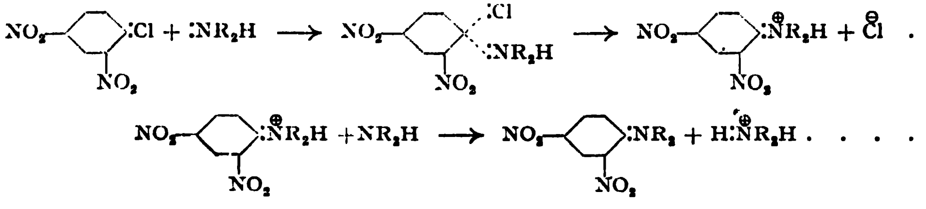
THE reaction between primary and secondary amines and 1-chloro-2 : 4-dinitrobenzene

$$2NHRR' + C_6H_3Cl(NO_2)_2 \longrightarrow C_6H_3(NO_2)_2{\cdot}NRR' + NH_2RR'Cl$$

produces only the substituted dinitroaniline and amine hydrochloride. The dinitrophenylalkylamine or dinitrophenyldialkylamine does not react further with the chlorodinitrobenzene, and the hydrolysis or alcoholysis of the last-named compound is not appreciable. The reaction, therefore, has advantages for the study of the reactivity of amines.

A concentration of amine twice that of the chlorodinitrobenzene being used, the reaction, in alcohol, was found to be of the second order, and good rate constants (k_2) were obtained for all amines used except those which reacted very slowly.

The simplest method of representing the reaction is as a heterolytic, nucleophilic one of type (*b*) in Ingold's classification of the mechanisms of substitution at a saturated carbon atom (1) (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 604), followed by loss of proton from the first product to a second molecule of amine.


NO$_2$
:Cl + :NR$_2$H
NO$_2$
:Cl
:NR$_2$H
NO$_2$
:$\overset{\oplus}{N}$R$_2$H + $\overset{\ominus}{Cl}$
NO$_2$
:$\overset{\oplus}{N}$R$_2$H +NR$_2$H
NO$_2$
:NR$_2$ + H:$\overset{\oplus}{N}$R$_2$H

(1)

(2)

Since the dinitrophenyldialkylamines are very weak bases the rate-determining reaction will be (1).

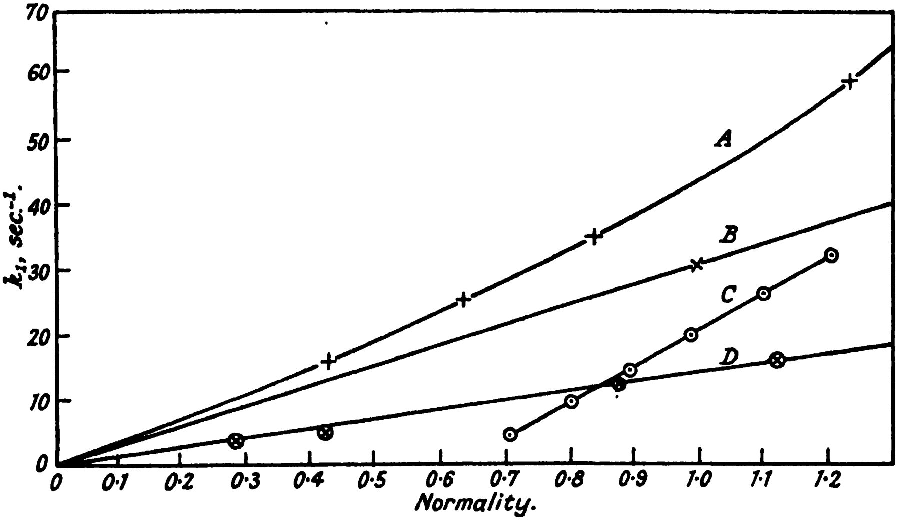
Possible secondary reactions are the following:

$$NHR_2 + HOEt \rightleftharpoons \overset{\oplus}{N}H_2R_2 + \overset{\ominus}{O}Et$$

$$(NO_2)_2C_6H_3Cl + \overset{\ominus}{O}Et \longrightarrow (NO_2)_2C_6H_3{\cdot}OEt + \overset{\ominus}{Cl}$$

$$(NO_2)_2C_6H_3{\cdot}OEt + NHR_2 \longrightarrow (NO_2)_2C_6H_3{\cdot}NR_2 + HOEt$$

Although alkoxyl ions act readily on 1-chloro-2 : 4-dinitrobenzene (Holleman and ter Weel, *Rec. Trav. chim.*, 1915, **35**, 1), their concentration under the conditions used cannot be sufficiently high for interference except in the cases of very slow-acting, fairly strongly basic amines such as *tert.*-butylamine or di*iso*propylamine (see Table I) since with a concentration of triethylamine (K_b = 6·4 × 10^{-4}) some twenty times that of the amine used in the study of the second-order reaction the liberation of chloride ion is exceedingly slow.



A, B, C, *Concn. of* NH$_2$Me. D. *Concn. of* NEt$_3$ *added to* 0·64N-NH$_2$Me.

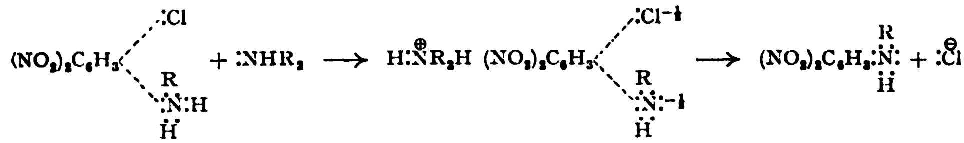
When the concentration of amine was far greater than that of the chlorodinitrobenzene the reaction became one of the first order or pseudo-unimolecular. The plot of the rate constant against concentration of amine is, however, not linear, the rate constant increasing more rapidly at higher concentrations of amines. The figure shows the plot of k_1^{25} against concentration of methylamine (*A*), the concentration of chlorodinitrobenzene being 0·329N., and of k_1' calculated from the second-order rate constant k_2^{25} by putting b, the concentration of methylamine, equal to unity (*B*).

Above 0·4N-methylamine the difference between the observed rate constant k_1 and the extrapolated value k_1' is proportional to the excess of methylamine over 0·4N. Curve *C* shows the plot of $k_1 - k_1'$ against concentrations of methylamine. One would expect this proportionality not to hold for concentrations of methylamine much below 0·4N., since this represents only six times the equivalent concentration of amine (0·0658N.) for the chlorodinitrobenzene, and the assumption necessary for using first-order kinetics is becoming of doubtful validity.

Triethylamine, which does not react to an appreciable extent with chlorodinitrobenzene under the conditions of experiment, also increases the rate constant when added to a reaction mixture containing 0·64N-methylamine, and the increase in the rate constant $(k_1'' - k_1)$ is proportional to the concentration of triethylamine. Curve *D* shows $(k_1'' - k_1)$/(concn. of NEt_3).

It is clear, therefore, that the velocity is influenced by a proton acceptor. Since the dinitrophenylalkylamines are very weak bases whose salts are practically completely hydrolysed in aqueous or alcoholic solution, reaction (2) is probably extremely rapid and we have to look elsewhere for the influence of the proton acceptor.

In the intermediate stage of (1) the presence of a proton acceptor will increase the electron availability of the nitrogen and facilitate its attachment to the carbon with the accompanying extrusion of the chloride ion :



This effect will be appreciable, probably, only when the concentration of amine is relatively high as in the pseudo-unimolecular reaction.

If the mechanism suggested for the bimolecular reaction be correct, the rate constant should depend upon the electron-availability at the nitrogen of the reacting amine, and electron-donating groups therein should increase the rate constant, which one would expect to bear a direct relation to the dissociation constants of the amine. The bimolecular rate constants (k_2^{25}) of the interaction between a number of amines with 1-chloro-2 : 4-dinitrobenzene in alcohol at 25° have been obtained by measuring the rate of liberation of chloride ion; the results are given in Table I, Col. 3.

The experimental part of this work was completed in 1935 and it was not until the results for the second-order reaction had been practically completed that it was discovered that Blanksma and Schreinemakers (*Rec. Trav. chim.*, 1933, **52**, 498) had published the rate constants for the reaction between 1-chloro-2 : 4-dinitrobenzene and a number of amines also in alcohol at 25° as measured by the rate of disappearance of amine. These are given in Table I, Col. 2, calculated to sec.$^{-1}$ from Blanksma and Schreinemakers's figures to min.$^{-1}$. Where the same amines were employed the results in Col. 2 and Col. 3 were obtained by different methods quite independently and the agreement in most cases is close. Even where there are appreciable discrepancies, *e.g.*, for piperidine, it does not affect the order of reactivity of the amines.

From a consideration of these results certain peculiarities are at once apparent. First, although the replacement of hydrogen by methyl, with the corresponding increase in basicity of the amine, leads to an increase in the rate constant ($k_2 \times 10^4$, NH_3 = 0·04, NH_2Me = 31·6, $NHMe_2$ = 355), yet in other cases the rate constants bear no obvious relation to the dissociation constants (K_b) of the amines. [The dissociation constants taken from the literature and given in Table I are for aqueous solutions, but it has been shown that their relative order is unchanged in passing from water to alcohol although their magnitude is greatly reduced (Goodhue and Hixon, *J. Amer. Chem. Soc.*, 1934, **56**, 1329).]

Secondly, one notices the high rate constant for methylamine ($k_2 \times 10^4$ = 31·6) compared with ethylamine ($k_2 \times 10^4$ = 9·1), for dimethylamine ($k_2 \times 10^4$ = 355) compared with diethylamine ($k_2 \times 10^4$ = 1·9), and for piperidine ($k_2 \times 10^4$ = 153) compared with ethyl-*n*-propylamine ($k_2 \times 10^4$ = 1·7) and α-pipecoline ($k_2 \times 10^4$ = 0·22).

Thirdly, whereas the rate constant for dimethylamine is about ten times that for methylamine, the rate constant for diethylamine is about one-fifth of that for ethylamine, and that for di*iso*propylamine about one-hundredth of that for *iso*propylamine.

TABLE I.

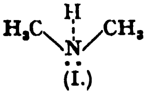
Amine.	$10^4 k_2^{25}$, sec.$^{-1}$, B. & Schr.	$10^4 k_2^{25}$, sec.$^{-1}$, B. & C.	$10^4 K_b$.	pK_H (25°).*
Dimethylamine	348	355	5·0	10·71
Piperidine	191	153	12·5	11·13
Methylamine	31·3	31·6	4·0	10·64
n-Heptylamine	10·2	10·0	—	—
n-Amylamine	10·1	—	—	10·64
n-Butylamine	9·5	10·0	—	10·61
n-Propylamine	8·9	9·6	3·9	10·58
Ethylamine	8·6	9·2	4·6	10·67
*iso*Butylamine	—	6·8	2·6	10·42
Diethylamine	1·8	1·9	10·0	10·98
Di-*n*-butylamine	—	1·8	—	11·31
Di*iso*amylamine	1·7	—	—	11·00
Ethyl-*n*-propylamine	—	1·7	—	—
Di-*n*-propylamine	1·6	1·6	8·2	10·91
*iso*Propylamine	1·1	1·0	4·3	10·63
sec.-Butylamine	0·92	0·91	3·6	10·56
Di*iso*butylamine	0·67	0·58	3·9	10·82
α-Pipecoline	—	0·22	—	10·98
Ethyl*iso*propylamine	—	0·18—0·033	—	—
Ammonia	0·04	0·04	0·18	9·27
tert.-Butylamine	—	0·038	3·4	10·45
Di*iso*propylamine	—	0·011—0·007	—	11·05
αα-Lupetidine	—	0·011—0·006	—	—
Tetrahydroquinoline	—	0·068—0·004	—	—
Tetrahydroquinaldine	—	0·004—0·002	—	—

* Negative log of hydrolysis constant (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469).

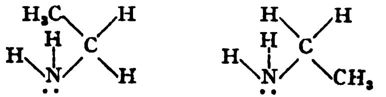
Fourthly, branching of the chain of the alkyl radical at the first carbon atom greatly reduces the rate constant ($k_2 \times 10^4$, *n*-propylamine = 9·6, *iso*propylamine = 1·0; *n*-butylamine = 10·0, *sec.*-butylamine = 0·92, *tert.*-butylamine = 0·038), but there is much less difference between *n*-butylamine ($k_2 \times 10^4$ = 10·0 and *iso*butylamine ($k_2 \times 10^4$ = 6·8).

In the light of these results it seems that the arrangement in space of the atoms of the alkyl groups in the amines plays an important part in determining their reactivity towards chlorodinitrobenzene.

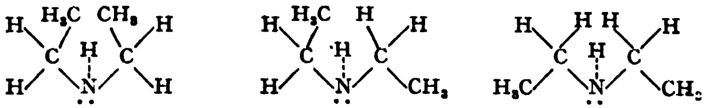
If one considers the stereochemistry of methylamine and ethylamine it will be seen that, whereas in methylamine and dimethylamine (I) there is at all times ample room for the approach of the large chlorodinitrobenzene molecule to the exposed part of the nitrogen atom, yet in the case of ethylamine, if there is free rotation about the carbon–nitrogen bond, at some time the methyl group can interfere with the approach of the chlorodinitrobenzene (II*b*). With diethylamine the time during which this steric hindrance will be effective will be greater (III*b*, III*c*).



(I.)



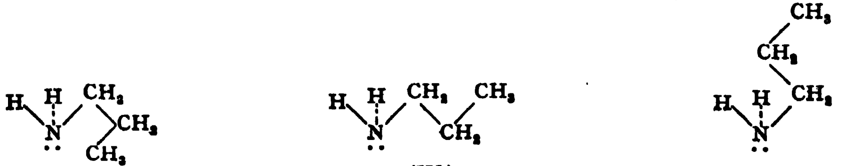
(*a*.) (II.) (*b*.)



(*a*) (*b*) (*c*)

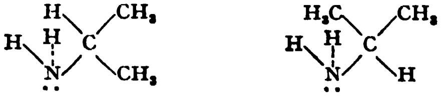
(III.)

Some of the possibilities with higher alkyl groups are shown in (IV).

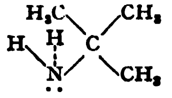


(IV.)

Branching at the first carbon atom of the alkyl chain will increase the time during which steric hindrance is effective; in *iso*propylamine (V) the time at which a methyl will exert a steric hindrance will be twice that in ethylamine, whilst in *tert.*-butylamine (VI) a methyl group will at all times interfere.

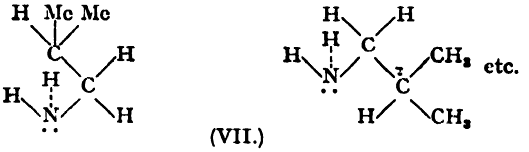


(V.)

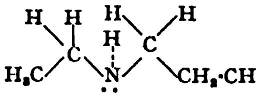


(VI.)

The effect of two *iso*propyl groups would be greater than that of one. The methyl in the *iso*butyl group would not have the same effect (VII), and *iso*butylamine might be expected to show similar results to *n*-butylamine.



(VII.)

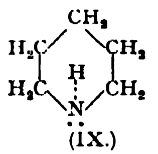


(VIII.)

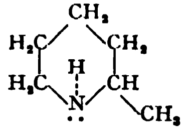
Since the basicity of the amine depends on the position of the equilibrium $NH_2R + \overset{\oplus}{H} \rightleftharpoons \overset{\oplus}{N}H_3R$, it would not be affected by steric influences.

The rate constants are all in agreement with the above views.

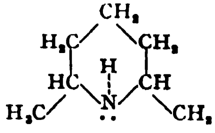
Confirmation is afforded by a consideration of ethyl-*n*-propylamine (VIII), piperidine (IX), pipecoline (X), and lupetidine (XI).



(IX.)



(X.)



(XI.)

In the first case the rate constant is low ($k_2 \times 10^4 = 1{\cdot}7$) and of the order of that for diethylamine, since at some time a steric effect can be exerted; when the carbon atoms take part in ring formation the state of affairs shown in (VIII) cannot occur and the rate constant for piperidine ($k_2 \times 10^4 = 153$) is of the same order as that of dimethylamine; the introduction of a permanently hindering methyl group results in a greatly reduced rate constant for α-pipecoline ($k_2 \times 10^4 = 0{\cdot}22$). Lellmann (*Ber.*, 1890, **23**, 1388; 1891, **24**, 2104) observed qualitatively the abnormally slow rate of reaction of α-pipecoline with 1-chloro-2 : 4-dinitrobenzene compared with that of piperidine or β-pipecoline (the β-methyl group could not interfere sterically). Finally, the rate constant for αα-lupetidine, where there are two permanently hindering methyl groups, is so low ($k_2 \times 10^4 = 0{\cdot}011$—$0{\cdot}006$) as to prevent accurate measurement at the temperature employed for the other amines.

The foregoing explanation has been put forward on the assumption that perfectly free rotation exists about the carbon–nitrogen bond, but the study of the Raman spectra of, *e.g.*, such a compound as 1 : 2-dichloroethane, has suggested that there is some restriction of rotation even between two singly bound carbon atoms. The possibility that the terminal methyl group in ethylamine is preferentially situated near the exposed part of the nitrogen atom cannot be rejected; it might certainly be so if the polarity of the C–H bond in the alkylamines is in the direction $\overset{\ominus}{C}-\overset{\oplus}{H}$ but, as stated by Gent (*Quart. Reviews*, 1948, **2**, 381), knowledge of the polarity of the C–H bond in various situations is still small, so it would be unprofitable to speculate in this direction.

The rate constants for the bimolecular reaction between chlorodinitrobenzene and methylamine and dimethylamine have been determined at 25°, 30°, 35°, and 40°, and it was found that the plot of log k against $1/T$ was, in both cases, a straight line, so it was assumed that the Arrhenius equation held for the interaction of the other amines with chlorodinitrobenzene. The energies of activation and collision frequencies are given in Table II. With the exception of those for methylamine and dimethylamine, the results are probably not very accurate, as measurements were made at only two temperatures.

TABLE II.

Amine.	E, cals.	$B \times 10^{-5}$, sec.$^{-1}$.	Amine.	E, cals.	$B \times 10^{-5}$, sec.$^{-1}$.
Dimethylamine	9,340	1·7	Ethylpropylamine ...	13,000	5·8
Piperidine	10,200	4·7	Di-*n*-butylamine ...	14,200	48
Methylamine	10,700	2·3	*sec.*-Butylamine	14,800	67
Ethylamine	11,700	3·6	Di*iso*butylamine	14,800	42
n-Butylamine	11,700	3·9	*iso*Butylamine	15,500	1600
Diethylamine	12,650	3·7	*iso*Propylamine	15,900	475

The energies of activation are low and rise with the decline in the rate constant, but *iso*butylamine and to a smaller degree *iso*propylamine are exceptions.

EXPERIMENTAL.

Materials.—The amines were mostly purchased and purified by careful fractionation; methylamine, ethylamine, and dimethylamine were purified by recrystallisation of their hydrochlorides; the bases were liberated by concentrated potassium hydroxide, dried by passing through tubes packed with sodium hydroxide, and absorbed in the solvent.

Ethylpropylamine was prepared by heating 33% aqueous ethylamine with *n*-propyl chloride in a rotating autoclave at 125—150° for 24 hours and distilling the oil liberated by alkali; the fraction, b. p. 84—86°, was used. Ethyl*iso*propylamine was prepared similarly by using *iso*propyl bromide at 120—160° for 120 hours, the fraction of b. p. 70—74° being used. *tert.*-Butylamine was prepared by the Hofmann reaction on pivalamide and purified through the hydrochloride and by distillation, the fraction, b. p. 45—46°, being used. α-Pipecoline, αα-lupetidine, and tetrahydroquinaldine were prepared by reduction of α-picoline, αα-lutidine, and quinaldine; α-pipecoline was purified through the thiocarbamate (Ladenberg, *Annalen*, 1888, **247**, 62) and collected at 199°; αα-lupetidine was purified through its hydrochloride and collected at 127°; tetrahydroquinaldine was purified by the method of Pope and Peachey (*J.*, 1899, **75**, 1089) and collected at 154°/43 mm.

The 1-chloro-2 : 4-dinitrobenzene was crystallised from benzene. No attempt was made to employ alcohol completely free from water owing to the difficulty in preventing absorption of small quantities of water during the experiments. It was thought that changes in velocity would be greater as the alcohol approached purity, so one batch was employed for all experiments; this had a density of 0·788 at 25°, corresponding to 99% of alcohol.

Procedure.—The amine was dissolved in alcohol, and the strength and the concentration checked by titration with acid. Solutions of 1-chloro-2 : 4-dinitrobenzene were prepared by dissolving a weighed quantity in alcohol and dilution to the correct volume. The concentrations of chlorodinitrobenzene at time 0 were 0·0329N. or 0·0148N., obtained by using 25 c.c. of 0·986N- or 0·0444N-chlorodinitrobenzene. The concentrations of the amines at time 0 were 0·0658N. or 0·0296N., obtained by using 50 c.c. of 0·0986N or 0·0444N-amine. In these cases the concentration of amine was twice that of the chlorodinitrobenzene. Where excess of amine was used the concentrations varied from 0·2N. to 1·5N., obtained by using 50 c.c. of 0·3N- to 2N-amine.

In carrying out the reaction, 50 c.c. of the amine solution at 25° were mixed with 25 c.c. of the chlorodinitrobenzene solution, also at 25°, and the mixture was kept in a closed vessel in a thermostat. At known intervals 10 c.c. of the reaction mixture were removed with a pipette and run into a mixture of 5 c.c. of nitric acid and 25 c.c. of 0·017N-silver nitrate in a 100-c.c. measuring flask. The volume was made up to 100 c.c. with water, the whole filtered, and 50 c.c. of the filtrate were titrated with a standard solution of potassium thiocyanate, ferric alum being used as indicator.

For tetrahydroquinoline and tetrahydroquinaldine the above method could not be used owing to the formation of an intense red colour with ferric alum and nitric acid, so the excess of silver nitrate was titrated with potassium iodide, starch–nitrite indicator being used.

Results.

The Bimolecular Reaction.—Figures are given below for the bimolecular reaction, in some detail for methylamine, dimethylamine, and ethylamine, to indicate the agreement between the values found, and in summarised form for the other amines (Table III). In each case samples were taken at five or six time intervals and the variation in the constant was small in the more rapid reactions. In the very slow reactions, *e.g.*, *tert.*-butylamine, the constant diminished with time, and greater detail is given of this determination as an example.

Since two moles of amine to one of chlorodinitrobenzene were used and two moles of amine react with one mole of chlorodinitrobenzene, if a = concn. of chlorodinitrobenzene, $2a$ = concn. of amine then $dx/dt = k_2(a - x)(2a - 2x) = 2k_2(a - x)^2 = K(a - x)^2$; hence $K = x/ta(a - x)$, where $K = 2k_2$.

Methylamine.

0·0658N-NH_2Me, 0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time (secs.)	630	1800	3600	6030	9960	17,460
Decompn., %	13·56	27·76	43·83	57·12	68·49	79·39
$k_2 \times 10^4$	34·6	32·5	34·1	33·6	33·2	33·5

50% Decompn. at 4620 secs. Average $k_2 = 33·6 \times 10^{-4}$ sec.$^{-1}$.

0·0296N-NH$_2$Me, 0·0148N-C$_6$H$_3$Cl(NO$_2$)$_2$; 25°; in 99% alcohol.

Time (secs.)	1500	3150	4980	5790	12,810	84,240
Decompn., %	12·1	22·2	31·2	35·0	54·2	88·8
$k_2 \times 10^4$	31·0	30·6	30·7	31·4	31·2	31·8

50% Decompn. at 10,620 secs. Average $k_2 = 31{\cdot}1 \times 10^{-4}$ sec.$^{-1}$.
$t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}3$; ratio of concentrations 0·0329/0·0148 = 2·22.
The average of four determinations gave $k_2 = 31{\cdot}6 \times 10^{-4}$ sec.$^{-1}$.

0·0658N-NH$_2$Me, 0·0329N-C$_6$H$_3$Cl(NO$_2$)$_2$, in 99% alcohol.

At 30°.			At 35°.			At 40°.		
Time, secs.	Decompn., %.	$k_2 \times 10^4$.	Time, secs.	Decompn., %.	$k_2 \times 10^4$.	Time, secs.	Decompn., %.	$k_2 \times 10^4$.
900	20·7	44·2	1005	28·06	58·9	660	25·3	78·1
1800	33·76	43·1	1500	36·75	59·1	900	31·66	78·3
3000	46·0	43·2	3615	57·91	57·9	1200	38·41	79·1
4200	54·88	44·1	5820	69·41	59·3	1920	50·24	80·0
5400	60·36	42·2	8925	77·68	59·3	3006	61·63	81·3
7380	67·96	43·7				4500	70·49	80·7
	Average =	43·4		Average =	58·9		Average =	79·6

Dimethylamine.

0·0658N-NHMe$_2$, 0·0329N-C$_6$H$_3$Cl(NO$_2$)$_2$; 25°; in 99% alcohol.

Time, secs.	240	360	600	1686	2490
Decompn., %	35·23	45·67	58·72	80·11	85·85
$k_2 \times 10^4$	345	355	360	363	372

50% Decompn. at 435 secs. Average $k_2 = 359 \times 10^{-4}$ sec.$^{-1}$.

0·029N-NHMe$_2$, 0·0148N-C$_6$H$_3$Cl(NO$_2$)$_2$; 25°; in 99% alcohol.

Time, secs.	555	1290	2160	4890
Decompn., %	36·5	56·2	69·0	84·1
$k_2 \times 10^4$	352	337	348	366

50% Decompn. at 975 secs. Average $k_2 = 351 \times 10^{-4}$ sec.$^{-1}$.
Ratio $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}24$; ratio of concentrations = 2·22.

0·0658N-NHMe$_2$, 0·0329N-C$_6$H$_3$Cl(NO$_2$)$_2$, in 99% alcohol.

At 30°.			At 35°.			At 40°.		
Time, secs.	Decompn., %.	$k_2 \times 10^4$.	Time, secs.	Decompn., %.	$k_2 \times 10^4$.	Time, secs.	Decompn., %.	$k_2 \times 10^4$.
180	35·09	45·6	90	22·06	57·5	90	31·66	78·2
240	42·20	46·2	105	28·46	57·6	162	45·16	77·3
306	48·54	46·9	225	46·41	58·4	210	50·24	78·7
390	54·44	46·6	270	52·38	62·0	240	55·31	78·4
570	63·74	46·9	300	54·69	61·2	303	60·78	77·8
774	70·08	46·1	480	65·26	59·6	420	68·38	78·3
	Average	46·4		Average	59·4		Average	78·1

Ethylamine.

0·0658N-NH$_2$Et, 0·0329N-C$_6$H$_3$Cl(NO$_2$)$_2$; 25°; in 99% alcohol.

Time, secs.	3825	9825	17,685	26,820	40,170	87,780
Decompn., %	19·16	37·69	50·93	62·42	69·9	83·72
$k_2 \times 10^4$	9·4	9·3	8·9	8·8	8·8	8·9

50% Decompn. at 12,620 secs. Average $k_2 = 9{\cdot}1 \times 10^{-4}$ sec.$^{-1}$.

0·0296N-NH$_2$Et, 0·0148N-C$_6$H$_3$Cl(NO$_2$)$_2$; 25°; in 99% alcohol.

Time, secs.	6885	21,420	38,430	84,605	258,420
Decompn., %	16·0	36·5	50·6	69·7	87·6
$k_2 \times 10^4$	9·3	9·2	9·0	9·2	9·2

50% Decompn. at 36,600 secs. Average $k_2 = 9{\cdot}2 \times 10^{-4}$ sec.$^{-1}$.
Ratio $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}20$; ratio of concentrations = 2·22.

0·0658N-NH$_2$Et, 0·0329N-C$_6$H$_3$Cl(NO$_2$)$_2$; 35°; in 99% alcohol.

Time, secs.	1850	4500	6770	10,440	14,100	17,700
Decompn., %	17·9	34·0	47·33	54·68	62·04	66·64
$k_2 \times 10^4$	17·2	17·4	17·6	17·6	17·6	16·7

Average $k_2 = 17{\cdot}4 \times 10^{-4}$ sec.$^{-1}$.

tert*-Butylamine.*

0·0296N-NH_2Bu^t, 0·0148N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, hours	172·3	312·2	552·7	1296·2	1802·1	2502·2
Decompn., %	8·27	16·4	19·2	32·8	38·9	49·1
$k_2 \times 10^4$	0·0049	[0·0059]	0·0040	0·0035	0·0033	0·0034

Average k_2 = 0·0038 × 10^{-4} sec.$^{-1}$.

Time, hours	165·8	378·1	594	1483·8	2130·4	4027
Decompn., %	8·27	16·43	21·4	36·9	44·0	59·4
$k_2 \times 10^4$	0·0051	0·0049	0·0043	0·0037	0·0035	0·0034

Average k_2 = 0·0041 × 10^{-4} sec.$^{-1}$.

Diisopropylamine.

0·0658N-$NHPr^i_2$, 0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, mins.	15,880	30,223	67,940	85,117	110,860	286,689
Decompn., %	6·86	11·46	17·00	19·76	23·89	43·19
$k_2 \times 10^4$	0·012	0·011	0·0078	0·0073	0·0072	0·0067

Lupetidine.

0·0658N-Lupetidine, 0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Time, mins.	15,774	34,537	70,629	92,240	136,808	156,852
Decompn., %	6·41	12·86	18·73	20·66	25·66	32·15
$k_2 \times 10^4$	0·011	0·011	0·0082	0·0072	0·0064	0·0063

In the case of amines which react less rapidly than ammonia, *e.g.*, *tert.*-butylamine, di*iso*propylamine, and lupetidine (cf. above), there is a fall in the rate constant, rapid at first but then much slower. Probably these amines contain small amounts of more reactive amines which are removed in the first period of the reaction. With these very slowly reacting amines very small quantities of impurities would have a large effect in the first stage.

The Pseudo-unimolecular Reaction.—The results obtained are summarised in Table IV.

Addition of Triethylamine.—With 0·0329N-chlorodinitrobenzene and N-triethylamine in alcohol at 25° less than 2% of chloride ion was liberated after 6180 secs., and less than 10% after 1,737,000 secs. The results of addition of triethylamine in the first-order reaction are summarised in Table V.

TABLE III.

0·0658N-Amine, 0·0329N-$C_6H_3Cl(NO_2)_2$ in 99% alcohol.

	Temp. = 25°.		Temp. = 35°.		Average values.	
Amine.	Time, secs. × 10^{-1}.	$k_2 \times 10^4$, sec.$^{-1}$, extremes.	Time, secs. × 10^{-1}.	$k_2 \times 10^4$, sec.$^{-1}$, extremes.	$k_2^{25} \times 10^4$, sec.$^{-1}$.	$k_2^{35} \times 10^4$, sec.$^{-1}$.
n-Propylamine	396—7,418	9·4—9·8	—	—	9·6	—
n-Butylamine	160—3,543	9·8—10·1	540—1,746	18·8—19·5	10·0	19·2
n-Heptylamine	408—3,804	9·7—10·0	—	—	10·0	—
Diethylamine	1,575—17,340	1·9—1·9	780—9,426	3·7—4·0	1·9	3·8
Di-*n*-propylamine	1,620—43,638	1·5—1·7	—	—	1·6	—
Di-*n*-butylamine	1,746—28,182	1·8—1·9	1,326—10,974	3·9—4·1	1·8	4·0
Ethyl-*n*-propylamine	1,884—34,560	1·6—1·7	1,155—19,380	3·3—3·6	1·7	3·4
*iso*Butylamine	360—11,320	6·6—7·1	300—1,790	14·9—16·0	6·8	15·6
*iso*Propylamine	1,929—42,072	0·98—1·0	1,248—17,688	2·3—2·5	1·0	2·4
sec.-Butylamine	2,826—60,546	0·88—0·95	2,826—17,022	2·0—2·1	0·91	2·1
Di*iso*butylamine	630—61,020	0·56—0·60	8,940—26,710	1·3—1·4	0·58	1·3
Piperidine	42—219	153—158	22·5—136·5	264—275	153	269
a-Pipecoline	4,291 min.—44,673	0·21—0·25	—	—	0·22	—
Ammonia	4,090 min.—100,600	0·037—0·046	—	—	0·04	—
Ethyl*iso*propylamine	6,140 min.—105,066	0·014—0·0032 *				
,, ,,	4,266 min.—126,780	0·019—0·0031 *				
Tetrahydroquinoline	3,012 min.—109,657	0·068—0·006 *				
,, ,,	17,149 min.—161,517	0·021—0·0045 *				
Tetrahydroquinaldine	23,061 min.—119,654	0·004—0·002 *				

* In these cases there was a progressive fall of k_2 with time.

TABLE IV.

0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; 99% alcohol.

Amine.	Concn., N.	Time, secs.	Extremes of $k_1 \times 10^4$.	Average $k_1 \times 10^4$.
Methylamine	0·424	99—960	15·4—16·5	16·1
	0·634	90—1,026	25·3—26·3	25·6
	0·833	120—605	35·0—35·9	35·6
	1·227	60—420	58·2—62·8	59·4
Ethylamine	0·583	126—4,260	6·13—6·95	6·35
	0·840	150—3,120	10·3—10·8	10·5
	1·350	245—1,170	20·1—21·1	20·5
n-Propylamine	0·553	345—3,000	5·96—6·45	6·15
	0·687	630—3,570	7·51—7·85	7·66
	0·790	720—2,790	9·07—9·35	9·26
n-Butylamine	0·573	615—3,270	7·08—7·24	7·12
	0·730	330—2,850	9·08—9·84	9·37
	0·753	375—1,890	9·62—9·92	9·75
n-Heptylamine	0·700	330—2,430	9·53—9·72	9·61
Dimethylamine	0·450	64—190	177—191	183 *
	0·500	57—180	206—218	214 *
	0·580	60—180	252—260	256 *
Diethylamine	0·491	1,935—18,300	0·99—1·05	1·03
	0·573	1,935—17,280	1·21—1·28	1·22
Di-*n*-propylamine	0·347	1,575—39,060	0·53—0·55	0·54
	0·566	1,440—21,300	1·02—1·04	1·03
Di-*n*-butylamine	0·400	4,500—18,630	0·76—0·82	0·78
	0·483	2,835—24,672	0·92—0·98	0·96
	0·560	2,646—20,820	1·11—1·18	1·13
Ethyl-*n*-propylamine	0·373	2,340—15,750	0·67—0·71	0·69
	0·453	3,600—28,980	0·80—0·89	0·85
	0·555	3,006—20,160	1·02—1·09	1·07
*iso*Butylamine	0·640	303—1,815	5·45—5·93	5·75
	0·813	270—1,170	7·85—8·25	8·04
	1·000	1,860—4,260	10·4—11·1	10·7
*iso*Propylamine	0·647	1,515—19,110	0·86—0·93	0·88
	0·947	3,426—15,666	1·36—1·45	1·40
sec.-Butylamine	0·400	5,220—40,950	0·42—0·45	0·44
	0·600	9,000—25,200	0·50—0·52	0·52
Di*iso*butylamine	0·520	3,300—37,890	0·33—0·35	0·34
	0·650	2,703—34,260	0·44—0·46	0·45
0·0148N-$C_6H_3(NO_2)_2Cl$; 25°.				
Methylamine	0·634	180—1,020	25·0—26·4	25·6
	0·833	126—636	36·5—38·0	37·5
	1·227	60—360	62·0—79·5	69·3

* Approximate, as the reaction is too fast at 25° for satisfactory measurements.

TABLE V.

0·0329N-$C_6H_3Cl(NO_2)_2$; 25°; in 99% alcohol.

Amine.	Concn. of amine, N.	Concn. of NEt_3.	Time, secs.	Extremes of $k_1 \times 10^4$.	Average $k_1 \times 10^4$.
Methylamine	0·64	0·28	90—600	28·2—29·6	29·1
	,,	0·329	90—450	30·8—31·8	31·4
	,,	0·873	150—480	36·3—40·5	38·4
	,,	1·12	66—420	38·3—43·2	42·2
	,,	1·33	75—465	44·0—46·0	44·9
	,,	2·00	66—450	56·3—59·3	58·0
Ethylamine	0·84	0·607	165—1,800	13·7—13·9	13·9
n-Propylamine	0·687	0·633	180—2,895	10·1—10·8	10·4
n-Butylamine	0·730	0·633	360—2,580	10·7—10·8	10·8
Dimethylamine	0·500	0·660	65—180	256—275	268 *
Diethylamine	0·573	0·807	930—16,020	1·64—1·85	1·72
Di-*n*-propylamine	0·347	0·677	3,075—39,060	0·66—0·69	0·68
Di-*n*-butylamine	0·483	0·660	5,820—20,820	1·13—1·16	1·15
*iso*Butylamine	0·813	0·687	420—840	9·55—10·8	10·0
*iso*Propylamine	0·947	0·647	2,580—9,210	1·85—1·96	1·91
sec.-Butylamine	0·400	0·440	8,460—30,810	0·51—0·53	0·52
Ammonia	1·093	0·647	21,546—211,620	0·082—0·099	0·088

* Approximate.

A number of derivatives of dinitroaniline have been prepared in the course of the work. The residual solutions obtained from the interaction of *tert.*-butylamine and 1-chloro-2 : 4-dinitrobenzene were mixed, heated in the water-bath, cooled, and diluted with water. The precipitate on crystallisation from dilute alcohol gave yellow crystals of N-tert.-*butyl*-2 : 4-*dinitroaniline*, m. p. 119° (Found : C, 50·0; H, 5·5. $C_{10}H_{13}O_4N_3$ requires C, 50·2; H, 5·5%). Chlorodinitrobenzene (5 g.) and di*iso*propylamine (5 g.) were heated in a sealed tube at 100° for 30 days. The black mass was extracted with boiling alcohol, and the solid which separated on cooling after being twice crystallised from alcohol gave N-*diisopropyl*-2 : 4-*dinitroaniline* as golden-yellow needles, m. p. 127° (Found : C, 53·9; H, 6·2. $C_{12}H_{17}O_4N_3$ requires C, 53·9; H, 6·4%). Mulder (*Rec. Trav. chim.*, 1906, **25**, 109, 113) failed to obtain this compound by this method. Alcoholic solution of α-pipecoline (100 c.c. of N/3) and chlorodinitrobenzene (75 c.c. of N/10) were mixed and kept for 14 days. The solution was evaporated to small bulk and the solid which separated on crystallisation from alcohol gave orange-red crystals of N-α-*pipecolyl*-2 : 4-*dinitroaniline*, m. p. 67° (Found: C, 54·3; H, 5·6. $C_{12}H_{15}O_4N_3$ requires C, 54·1; H, 5·7%); Lellman (*loc. cit.*) described an impure specimen as an oil. Alcoholic solutions of tetrahydroquinoline (60 c.c. of N.) and chlorodinitrobenzene (250 c.c. of N/10) were heated to 100° and kept for two days, evaporated to small bulk, and the solid which separated crystallised from alcohol–benzene; N-*tetrahydroquinolyl*-2 : 4-*dinitroaniline* was obtained as yellow crystals, m. p. 155·5°, which became red on exposure to light (Found : C, 60·6; H, 4·4. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·4%).

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THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.
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100. *Inorganic Chromatography on Cellulose. Part II*. The Separation and Detection of Metals and Acid Radicals on Strips of Absorbent Paper.*

By F. H. BURSTALL, G. R. DAVIES, R. P. LINSTEAD, and R. A. WELLS.

A method for the separation and detection of a number of metallic ions and acid radicals by extraction with organic solvent mixtures on strips or sheets of absorbent paper is described. Detection is accomplished by spraying the strip or sheet of paper with a solution containing suitable reagents; the presence of individual metals or acid radicals is then made visible as characteristic coloured bands. The following groups of ions have been separated (R.E. = rare earths) :

(a).	(b).	(c).	(d).	(e).	(f).	(g).	(h.)	(i).	(j).
Pb^{2+}	As^{3+}	Fe^{3+}	Ni^{2+}	Pt^{4+}	R.E.$^{3+}$	SeO_3^{2-}	Li^+	Ca^{2+}	F^-
Cu^{2+}	Sb^{3+}	Al^{3+}	Mn^{2+}	Pd^{2+}	Sc^{3+}	TeO_3^{2-}	Na^+	Sr^{2+}	Cl^-
Bi^{3+}	Sn^{2+}	Cr^{3+}	Co^{2+}	Rh^{3+}	Th^{4+}	—	K^+	Ba^{2+}	Br^-
Cd^{2+}	—	—	Zn^{2+}	Ir^{4+}	—	—	—	—	I^-
Hg^{2+}	—	—	Cu^{2+}	Ir^{3+}	—	—	—	—	—
			Fe^{3+}	Ru^{4+}					
			UO_2^{2+}	Ru^{3+}					
			VO_3^+	Os^{4+}					
			Ti^{4+}	Au^{3+}					

The ratio of the distances moved by the ion to that moved by the solvent (R_F value) has been determined in a number of cases. The significance of these measurements is discussed.

WE have already given a preliminary account of the separation of inorganic salts by the technique of paper chromatography employing organic solvents (Report of the Chemistry Research Board 1947, H.M.S.O.; Arden, Burstall, Davies, Lewis, and Linstead, *Nature*, 1948, **162**, 691; Burstall, Davies, Linstead, and Wells, *ibid.*, 1949, **163**, 64; Linstead, *ibid.*, p. 598). Observations made in other laboratories have also recently been described (Lederer, *Nature*, 1948, **162**, 776; Pollard, McOmie, and Elbeih, *ibid.*, 1949, **163**, 292; Lederer, *ibid.*, p. 598; Lacourt, Sommereyns, Degeyndt, Baruh, and Gillard, *ibid.*, p. 999; Lederer, *Anal. Chim. Acta*, 1948, **3**, 476; *idem*, *Science*, 1949, **10**, 115; Osborne and Jewsbury, *Nature*, 1949, **164**, 443).

The following account provides a more detailed description of the qualitative separations carried out in this laboratory; quantitative separations will be the subject of a further paper. Methods of separating the metals constituting the ordinary qualitative analytical groups are described and the isolation of the constituents of mixtures containing some of the less common metals is also included. A few separations of anions have also been achieved. In some cases a particular separation has been extensively studied as to repeatability and interference by various factors (see, *e.g.*, Part I, *loc. cit.*); in others the method is at a much earlier stage of development.

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* Part I is regarded as the paper by Arden, Burstall, and Linstead (*J.*, 1949, S 311).

Paper chromatography has certain advantages over the conventional methods of qualitative inorganic chemical analysis—it is simple and reasonably rapid, costly special apparatus and chemicals are not necessary, and only small quantities of material are required for test purposes. Moreover, the method has proved successful for the separation and detection of groups of metals which are difficult to deal with by existing procedures, *e.g.*, the separation of the platinum metals from one another, of scandium from the rare earths and thorium, and of calcium, strontium, and barium from each other.

The technique is particularly useful in the separation and detection of groups of elements obtained by some suitable pretreatment of a complex mixture. The well-known analytical groups form a useful division of this kind; the further separation and detection of the elements in these groups can then be conveniently carried out by the methods now described.

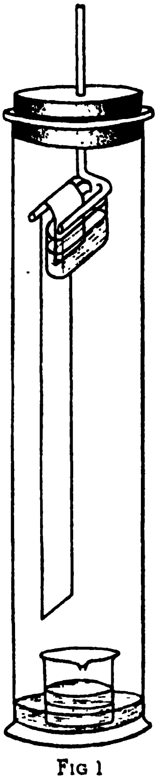


FIG 1

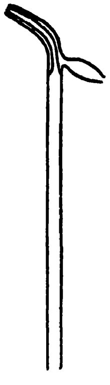


FIG 2

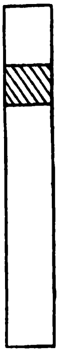


FIG 3

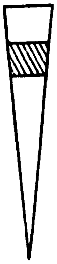


FIG 4.

It seems quite possible, also, that a complete system of qualitative chemical analysis could be developed on the basis of this new technique. The method is capable of giving good results in the hands of relatively inexperienced chemists. Separations, simple and easy to carry out, include Group IIa (Pb, Cu, Bi, Cd, and Hg), Group IIIb (Co, Ni, Mn, and Zn), the platinum metals and gold. More difficult separations are found in Group IIb (As, Sb, and Sn) and Group IV (Ca, Sr, and Ba). In routine operations such as are employed extensively in industry, the method should be particularly valuable since the conditions can be arranged to cover a particular series of metals or acid radicals and the procedure does not require continuous attention by a chemist.

EXPERIMENTAL.

Nearly all the experiments described in this paper were carried out on paper strips by a procedure which resembles, in general, that employed in similar organic work (Consden, Gordon, and Martin, *Biochem. J.*, 1944, **38**, 224). In view of the general interest of the method in the inorganic field, we give below a description of the technique which has been found most satisfactory over the past 4 years. The apparatus (Fig. 1) consists of a tall glass gas-jar closed with a tight fitting cork or a rubber bung which carries a glass rod to which is attached a glass boat. The boat is suspended about an inch below the bottom of the cork and serves as the container for the solvent employed in the separations. Two side arms are fused to the glass rod above the solvent container and these act as supports for a pair of paper strips, one strip being shown in position in the figure. In order to saturate the atmosphere in the cylinder with respect to the solvent, a layer of the latter is kept at the bottom of the cylinder. In some cases it is also necessary to control the amount of water vapour or acid in the atmosphere and for this purpose a beaker containing water, saturated salt solution, or aqueous acid saturated with solvent is placed on the bottom of the jar. It is advantageous also to maintain fairly constant temperature conditions, and in some cases the whole apparatus is kept in a thermostatically controlled (±1°) cabinet or bath.

The method of preparing the paper strip is substantially the same as in the earlier description (Arden, Burstall, Davies, Lewis, and Linstead, *loc. cit.*). A convenient volume (0·05 ml.) of the solution to be tested is placed near one end of a strip of filter-paper. This forms a wet patch about one inch square (Fig. 3) which is usually allowed to dry completely in air although in some cases the degree of drying is dependent on the chemical stability of the salts undergoing separation. In spite of the fact that the original solution is allowed to spread completely across the strip, little trouble has been experienced with edge effects. The strip is then hung vertically in the cylinder with the upper end immersed in the solvent contained in the glass boat. After the solvent has diffused down the paper a sufficient distance to effect a separation, the strip is removed from the cylinder, the solvent is allowed to evaporate, and the presence and position of the salts on the strip are determined by spraying with a suitable reagent. A simple type of atomiser suitable for this purpose is shown in Fig. 2. A large number of inorganic and organic reagents have been used. The criteria applied in choosing a developing reagent differ from those usually employed in selecting a spot-test reagent. It is not necessary for the reagent to be specific for a certain radical, but it is desirable to have one which will give a delicate test for as many radicals as possible. Some of the reagents found particularly useful in this respect are diphenylthiocarbazone (dithizone), diphenylcarbazide, alizarin, rubeanic acid, salicylaldoxime, and morin. In many cases mixtures of two or more of these reagents are advantageous.

In order to obtain repeatable results it is necessary to be certain of constancy in composition of the solvents employed. In many cases, particularly with water-miscible solvents, small variations in the water content will alter considerably the efficiency of a separation. All the solvents used have received a suitable pretreatment which is described later.

The separations described below have been carried out on Whatman No. 1 or No. 3 filter-paper but a number of other papers have been used successfully. The length of the paper strip has varied from about 9 to 18 inches and, although usually this has been about 1 inch in width, it is useful in the detection of small quantities of material to employ a triangular strip as shown in Fig. 4, so that the extracted substance is concentrated in a smaller area of paper.

In the following description of various separations which have been made, a short note of the method recommended for each separation is recorded at the beginning of the appropriate section; this is then followed by a detailed consideration of the behaviour of the metals or acid radicals.

(a) *Analytical Group IIa* : Pb, Cu, Bi, Cd, *and* Hg. (With D. B. REES EVANS.) *Recommended method.* The metals are present as chlorides and the solvent used is *n*-butyl alcohol saturated with 3N-hydrochloric acid.

In earlier work (Burstall, Davies, Linstead, and Wells, *loc. cit.*) it was found that lead, copper, bismuth, cadmium, and mercury can be separated by the use of ethyl *iso*propyl ketone containing 10% (v/v) hydrochloric acid (*d* 1·18). These two liquids are not completely miscible, but one phase is obtained on addition of small amounts of *iso*propyl alcohol or larger amounts of methyl alcohol. Better separations are possible, however, with other solvents described below.

Separation of copper, lead, bismuth, cadmium, and mercury was achieved by using butyl alcohol or amyl alcohol saturated with aqueous hydrochloric acid as solvent. The degree of separation obtained depended on the concentration of the aqueous acid used (Fig. 5). Butyl alcohol saturated with 3N-hydrochloric acid was found to give the most efficient separation. It was prepared by shaking together equal volumes of the alcohol and 3N-hydrochloric acid, the top layer being used. A solution of the metals in dilute hydrochloric acid was spotted on a strip of paper which had to be at least 18″ long to obtain a good separation of copper and lead. The spot was allowed to dry in air for one hour. Use of a wet spot gave wider bands and a more rapid movement of solvent down the strip but did not much affect the R_F values of the five metals. The solvent was allowed to flow for 15—18 hours in an atmosphere saturated with respect to both organic solvent and aqueous phases. After evaporation of the solvent, the strip was sprayed with a solution of dithizone in chloroform. Mercury was detected as a pink band behind the solvent front and was followed by cadmium as a purple band. Although cadmium and mercury were not in the solvent front and each metal was separated from the other, both bands had sharp leading and trailing edges with a width less than that of the original spot. Bismuth appeared as a purple, and copper as a purplish-brown band. Lead, which gives only a weak colour with dithizone, was detected by spraying the top portion of the strip with an aqueous solution of rhodizonic acid; a bright blue band due to lead then appeared just below the copper.

A number of different effects was noted on varying the concentration of the acid with which the butyl alcohol was saturated. As the acidity was decreased, (*a*) the bands of all five metals became more diffuse (this effect was most marked with bismuth), (*b*) the R_F value of each cation decreased but to a different extent for each metal. This resulted in a better separation of cadmium and mercury which was partly counteracted by an increase in band width and a decrease in the degree of separation of copper and lead. No complete separation of copper and lead was achieved, even after 18 hours, when acid of strength less than 3N. was used. A series of R_F values obtained by using different acidities is shown in Table I. For the purpose of these measurements an R_F value is taken as the ratio of the distance moved by the " centre of gravity " of a band to the distance moved by the solvent.

TABLE I.

Variations in R_F *values with change in acid concentrations.*

Solvent.	Cu.	Pb.	Bi.	Cd.	Wet solvent front.	Hg.
Satd. with H_2O	0·04, 0·04	0·05, 0·05	0·50, 0·49	0·60, 0·62	0·65, 0·66	0·73, 0·74
Satd. with 1N-HCl ...	0·08, 0·08	0·12, 0·11	0·55, 0·52	0·66, 0·63	0·70, 0·68	0·76, 0·78
Satd. with 2N-HCl ...	0·13, 0·11	0·17, 0·12	0·57, 0·54	0·69, 0·66	0·72, 0·69	0·76, 0·76
Satd. with 3N-HCl ...	0·20, 0·20	0·27, 0·27	0·60, 0·58	0·77, 0·77	0·79, 0·79	0·81, 0·81

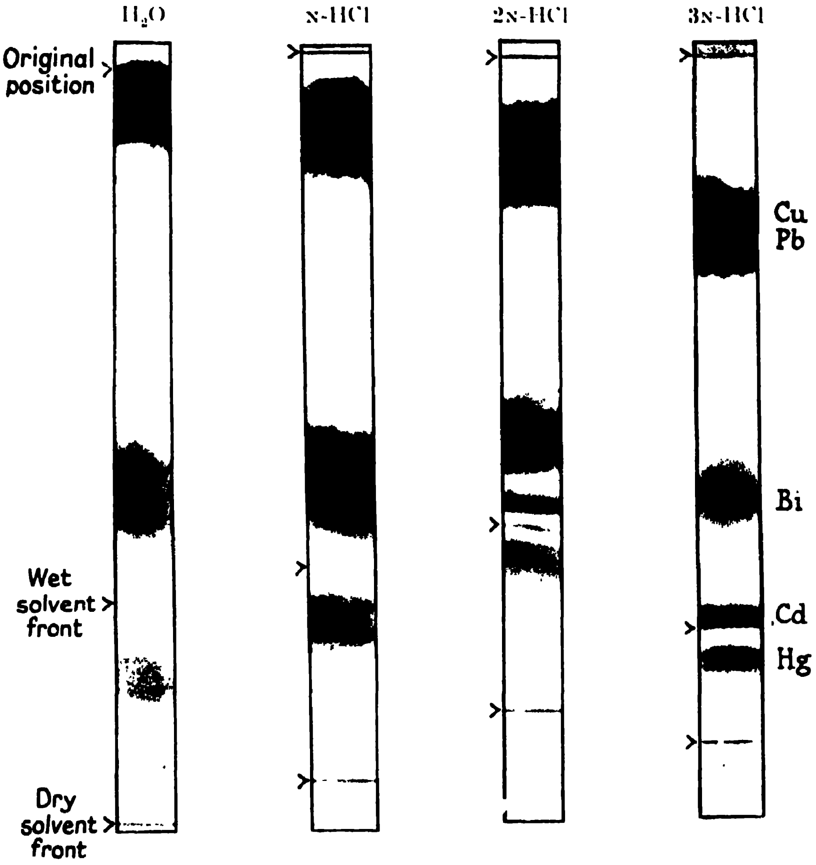
Two solvent phases exist on the paper strip, an upper area in which the paper is saturated with water and below that a region of dry solvent. When the solvent contained both hydrochloric acid and water the upper wet phase was strongly acid, but the lower dry phase was almost free from acid. The boundary between these two phases was not easily detected until the strip was sprayed with a suitable reagent, but on spraying the strip with dithizone or diphenylcarbazide solution a band of what appeared to be cadmium was found just in front of the main cadmium band. A similar band was obtained when a blank strip of paper was used and did in fact mark the position of the wet solvent boundary. The material causing the colour has not been identified but appears to be organic rather than inorganic since it gives a negative test for metals such as copper and iron normally found in cellulose. The position of the wet solvent front was also found by taking advantage of the difference in acidity of the two phases and spraying the strip with a suitable indicator. The R_F value of the wet solvent front was measured in a number of cases and is recorded in Table I.

As the concentration of aqueous acid used was increased above 3N-hydrochloric acid the bismuth and

Fig. 5.

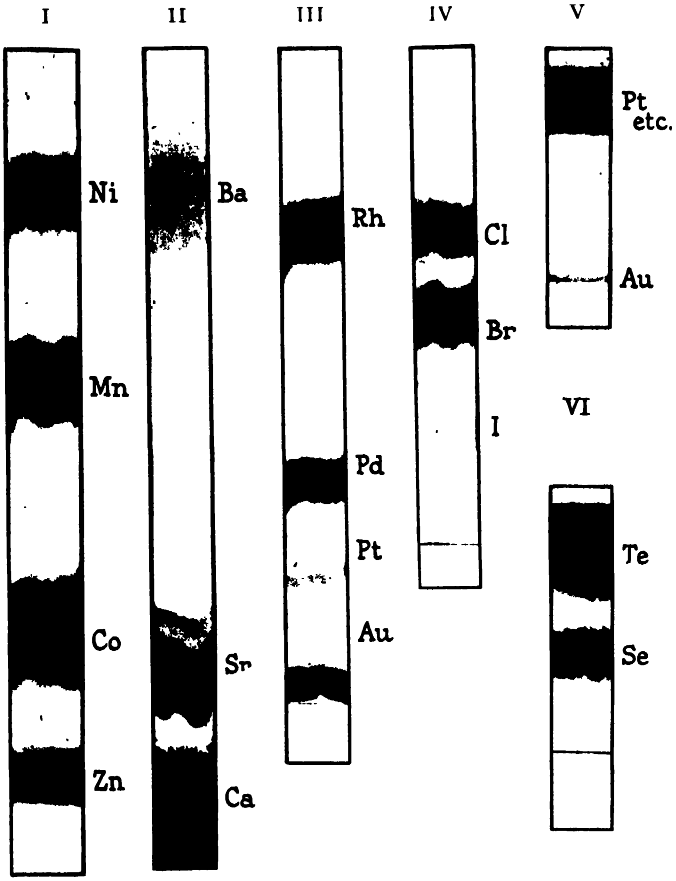
Group IIa.

Solvent: Butyl alcohol saturated with



[*To face p.* 518.

FIG. 6.



lead bands were displaced backwards towards the copper whereas the cadmium band moved forward towards the mercury. The use of butyl alcohol containing 10% (v/v) of hydrochloric acid (*d* 1·18) resulted in mercury and cadmium being found in a mixed band. Copper and bismuth also formed a mixed band but lead was now in a separate band behind the copper. In order to get repeatable figures for R_F values it was essential that the atmosphere be completely saturated with respect to butyl alcohol and aqueous acid phases. Well-separated bands of bismuth, cadmium, and mercury were often obtained when at the beginning of a run the atmosphere was incompletely saturated, but results were not accurately repeatable. As an aid to maintaining a constant atmosphere the temperature was controlled at 22°. The R_F values appeared to be fairly independent of the concentration of each of the metals, of the total concentration of metals, and of the acid concentration of the original solution. Bismuth was more affected by such factors than the other metals. A difference in R_F values was noted in tests with varying times of solvent diffusion. Table II gives R_F values obtained with butyl alcohol saturated with aqueous acid of different strengths. The effect of time of running is noticeable in each case but agreement between duplicate strips is good. Unless otherwise stated, the amount of copper, bismuth, cadmium, and mercury was 100 μg. of each metal, and 40 μg. of lead were used.

TABLE II.

R_F *Values using butyl alcohol* + 3N-HCl.

Metal.	Time of run.						
	7 hrs.	8 hrs.		15 hrs.		16 hrs.	
Cu	0·10	0·21	0·21	0·24	0·25	0·25	0·25
Pb	0·24	—	—	0·30	0·30	—	—
Bi	0·56	0·58	0·60	0·69	0·70	0·74	0·73
Cd	0·71	0·69	0·70	0·87	0·89	0·89	0·88
Hg	0·80	0·73 *	0·75 *	0·91	0·92	0·92 *	0·92 *

* Only 10 μg. of Hg present.

R_F *Values using butyl alcohol* + 2·5N-HCl.

Metal.	Time of run.							
	5 hrs.		8 hrs.		16 hrs.		16 hrs.	
Cu	0·15	0·17	0·15	0·16	0·18	0·19	0·19	0·19
Bi	0·55	0·54	0·58	0·55	0·63	0·63	0·62	0·62
Cd	0·66	0·66	0·67	0·65	0·73	0·73	0·73	0·72
Hg	0·73	0·72	0·77	0·75	0·79	0·78	0·78	0·76

R_F *Values using butyl alcohol* + 2N-HCl.

Metal.	Time of run.							
	5 hrs.		8 hrs.		16 hrs.		16 hrs.	
Cu	0·15	0·13	0·13	0·13	0·16	0·15	0·14	0·14
Bi	0·53	0·52	0·54	0·54	0·60	0·58	0·58	0·58
Cd	0·62	0·61	0·64	0·62	0·70	0·68	0·67	0·64
Hg	0·70	0·71	0·73	0·74	0·75	0·75	0·74	0·72

TABLE III.

R_F *Values with different solvents prepared with* 2·5N-HCl.

Metal.	Method (*a*).		Method (*b*).		Method (*c*).	
Cu	0·17	0·18	0·19	0·20	0·16	0·15
Pb	0·25	0·25	0·27	0·27	0·20	0·20
Bi	0·59	0·63	0·63	0·65	0·64	0·62
Cd	0·68	0·73	0·75	0·76	0·75	0·73
Hg	0·74	0·80	0·79	0·80	0·81	0·79

The term " butyl alcohol saturated with hydrochloric acid " is capable of several interpretations, but from the R_F values given in Table III it will be seen that no significant difference is made to the separation when three different methods are used for saturating the solvent: (*a*) by shaking together equal volumes of acid and butyl alcohol, (*b*) by shaking two volumes of acid and one of butyl alcohol, (*c*) by adding acid to butyl alcohol until two phases just do not separate.

A similar pattern in the results was obtained by using amyl alcohol in place of butyl alcohol. The optimum concentration of aqueous hydrochloric acid used for saturating the alcohol was again 3N. A similar two-phase effect was observed, as was found with butyl alcohol. One marked difference obtained with amyl alcohol was an absence of separation between copper and lead. A large number of variations in the solvent mixture was tried in order to achieve a separation but without success.

As the acid concentration was increased beyond 3N., the same closing up of the bands (already described for butyl alcohol) was observed. If the hydrochloric acid concentration was raised until the amyl alcohol contained 20% (v/v) of hydrochloric acid (*d* 1·18), lead was obtained as a separate band above the copper. The R_F values obtained on using amyl alcohol which had been shaken with an equal volume of 3N-hydrochloric acid are given in Table IV. Temperature was again controlled at 22° and time of running was 18 hours.

TABLE IV.

R_F *Values using amyl alcohol + 3*N-*hydrochloric acid.*

Metal.	Cu.	Bi.	Cd.	Hg.
R_F value	0·07, 0·07	0·36, 0·36	0·63, 0·64	0·70, 0·72

Copper, bismuth, cadmium, and mercury have been separated from lead by using methyl alcohol containing 5% (v/v) of concentrated hydrochloric acid as solvent. The solution of the metals in dilute hydrochloric acid was spotted on a strip and allowed to dry thoroughly in air. The copper, bismuth, cadmium, and mercury travel in mixed diffuse bands with mercury in the solvent front, while the lead moves much more slowly. A lower concentration of hydrochloric acid in the solvent results in a diffuse lead band, whereas higher concentrations cause the lead to move sufficiently fast to overlap the copper.

Another separation of Group IIa metals has been achieved by using pyridine. Bismuth, copper, cadmium, and mercury have been separated in that order. Lead and bismuth remained in the original spot while mercury was just in front of, but overlapping, the cadmium. The original solution of the metals in dilute hydrochloric acid was spotted on a paper strip and then made alkaline by exposure to ammonia vapour. A better separation was achieved by this method than by leaving the original spot acid.

(b) *Analytical Group IIb*: As, Sb, *and* Sn. (With N. F. KEMBER.)—*Recommended method.* The metals are present as their lower chlorides and the solvent consists of a mixture of acetylacetone saturated with water, with 0·5% (v/v) of hydrochloric acid (*d* 1·18) and 25% (v/v) of acetone.

A very large number of solvents have been examined for the separation of arsenious, antimonous, and stannous chlorides. Many solvents gave a clear-cut separation of antimony and tin from arsenic, but few have been found capable of completely separating antimony and tin. Development with gaseous hydrogen sulphide was used in early tests as a means of detecting the arsenic, antimony, and tin bands; it then appeared possible to separate antimony and tin with a number of solvents. The use of a chloroform solution of dithizone, which was a more sensitive spot test, showed that, while most of the tin appeared to be in a concentrated band separated from antimony, a small amount of tin tailed back to the front edge of the antimony. The separation of arsenic, antimony and tin using ethyl acetate (Burstall, Davies, Linstead, and Wells, *loc. cit.*) suffers from the same disadvantage. The best conditions for obtaining repeatable results with ethyl acetate were as follows. The original solution of the metals in dilute hydrochloric acid was spotted on to a paper strip and allowed to dry in air for 1 hour. The strip was then tested as already described with ethyl acetate saturated with water in an atmosphere of ethyl acetate and water vapour. After evaporation of the solvent the strip was sprayed with a solution of dithizone in chloroform. The arsenic was detected as a very sharp, narrow, yellow band, while the antimony was lower down the strip in a wider reddish band with sharp front and rear edges, and the tin formed a purple band, with a sharp front edge and a trailing rear edge well behind the solvent front. Similar results were obtained with methyl acetate and methyl propyl ketone. Various modifications were tried in order to obtain a better tin band, *e.g.*, (*a*) addition of ethyl acetoacetate to ethyl acetate, (*b*) the use of methyl acetate in an atmosphere of chloroform vapour, (*c*) addition of chloroform to methyl acetate, (*d*) addition of various concentrations of hydrochloric acid and water to : methyl propyl ketone; methyl propyl ketone–acetone mixtures; methyl acetate–acetone mixtures, etc. A good separation of all three metals was sometimes obtained, but results with respect to the tailing of the tin band were difficult to repeat. Of the alcohols tried, butyl alcohol saturated with water gave the best separations. Antimony and tin were well separated from arsenic, which formed a more diffuse band than that obtained with esters or ketones. Both antimony and tin furnished very narrow bands which, in an atmosphere saturated with the solvent, were very close together or just touching. Addition of hydrochloric acid to the alcohol resulted in overlapping of the antimony and tin bands. Good bands were obtained for all three metals on using ethyl ether saturated with water, but again the antimony and tin bands touched. Other solvents examined include: acetone, methyl ethyl ketone, *cyclo*hexanone, *iso*propyl ether, " Cellosolve " and its derivatives, pyridine, 2 : 2′-dichlorodiethyl ether, methyl *iso*butyl ketone, dioxan, formic acid, acetic acid, triacetin, and ethylene dichloride.

Acetylacetone gave the best separation of tin and antimony so far achieved. Separations were first obtained by using acetylacetone saturated with water. There was a tendency, also found with other solvents, for a small amount of tin to remain behind in the original spot. To prevent this effect 0·5% (v/v) of hydrochloric acid (*d* 1·18) was added to the solvent together with 25% (v/v) of acetone. The acetone was added in amount sufficient to enable the hydrochloric acid and acetylacetone to form a clear solution. The acetylacetone was freshly distilled, and the fraction of b. p. 137—141° was collected. This fraction was saturated with water, and to 7·5 ml. of the saturated solvent were added 0·05 ml. of concentrated hydrochloric acid and 2·5 ml. of dry acetone. A solution of arsenious, antimonous, and stannous chlorides in dilute hydrochloric acid (2—4N.) was spotted on a paper strip and allowed to dry in air for 15 minutes. The experiment was then run with this solvent for one hour (solvent movement 15 cm.) in an atmosphere saturated with respect to a saturated solution of acetylacetone in water. The complexes formed with acetylacetone were extremely stable, particularly the one formed with tin. Accordingly, the following method was used to develop the bands: the strip was removed from the extraction vessel, and the solvent allowed to evaporate for several minutes. Before the strip was completely dry it was sprayed with a chloroform solution of dithizone and then allowed to dry thoroughly. The tin was found in the solvent front and had a diffuse trailing edge. The antimony formed a wider band with a sharp front and slightly diffuse rear edge; approximate R_F value 0·5. The arsenic was present in a very narrow band; R_F value approx. 0·2.

(c) *Analytical Group IIIa*: Fe, Al, *and* Cr.—*Recommended method.* The metals are present as chlorides and the solvent used is glacial acetic acid containing 25% (v/v) of dry methyl alcohol.

Although the separation of iron from aluminium and chromium can be carried out easily with a large number of solvents, the separation of aluminium from chromium was more difficult. A convenient solvent for the separation of iron as ferric chloride from aluminium and chromic chlorides was acetone containing hydrochloric acid. The acid concentration was not critical but acetone +10% (v/v) of hydrochloric acid (*d* 1·18) produced a narrow band of iron in the solvent front with little movement of aluminium and chromium. Increase in the acid or water content of the acetone resulted in increased movement of aluminium and chromium but always in overlapping bands. A large number of solvents were tested for the separation of aluminium and chromium including : methyl, ethyl, *iso*propyl, butyl, and amyl alcohols, methyl propyl ketone, ether, *iso*propyl ether, "Cellosolve," "Carbitol," ethyl acetate, and pyridine. These solvents were tested with varying concentrations of water and hydrochloric acid and in mixtures of these liquids. Separation of aluminium and chromium was not obtained although movement of both metals often took place. In all these experiments the original solution consisted of a solution of ferric, aluminium, and chromic chlorides in dilute hydrochloric acid. Chromium as chromate or dichromate was extremely soluble in organic solvents but reduction to chromic chloride occurred, resulting in a diffuse band of chromium stretching from the solvent front to the original spot.

Aluminium as the trichloride was extracted in the solvent front by aqueous acetic or formic acid solutions (Lacourt *et al.*, *loc. cit.*). With glacial acetic acid, aluminium and chromium moved slightly and together, and iron was extracted in a band some way behind the solvent front. As the concentration of water in the solvent was increased, so did the rate of movement of the three metals, the movement of aluminium being much greater than that of chromium and iron. If a mixture of equal volumes of glacial acetic acid and water was used as solvent, aluminium was found in the solvent front, with iron in a separate band just behind the aluminium, and chromium still further behind, but only just separated from iron. By adjusting the water concentration it was possible to obtain a separation of chromium, aluminium, and iron in that order, proceeding down the strip. Such a separation was achieved by the use of acetic acid containing 10% (v/v) of water but the bands were all very diffuse.

The same type of variation in movements obtained with acetic acid–water mixtures was also obtained with acetic acid–methanol and acetic acid–ethanol mixtures. With these mixtures better bands were obtained and there was less tendency for the formation of the double bands of chromium and iron often obtained with aqueous acetic acid. The best separations were obtained with glacial acetic acid containing 25% (v/v) of dry methyl alcohol. The test solution of iron, aluminium, and chromium chlorides was prepared in 5N-hydrochloric acid, spotted on to a paper strip, and allowed to evaporate to dryness in air. Use of a solution containing insufficient free hydrochloric acid gave incomplete extraction and double-band formation of iron. The experiment was allowed to run for 12 hours in an atmosphere saturated with respect to the mixed solvents. A further improvement in the separation was obtained by maintaining a low humidity in the extraction chamber, *e.g.*, by keeping a saturated solution of potassium carbonate in the bottom of the vessel. In order to detect the position of the bands, the solvent was allowed to evaporate and the strip was cut lengthwise into two portions. One portion was sprayed with an alcoholic solution of alizarin, made alkaline by exposure to ammonia vapour, and then warmed. Aluminium appeared as a red band well separated from a purple band due to iron, which was some way behind the solvent front. The other portion of the strip was sprayed first with aqueous sodium peroxide solution and then with a solution of benzidine in acetic acid. Chromium was indicated as a bright blue band just behind the aluminium.

Unsuccessful attempts at separation were made when the nitrates of iron, aluminium, and chromium were used with solvents containing nitric acid or potassium thiocyanate.

(d) *Analytical Group IIIb* : Ni, Mn, Co, *and* Zn. (With Miss J. N. Clarke.)—*Recommended method.* The metals are present as chlorides, and the solvent used is acetone containg 5% (v/v) of water and 8% (v/v) of hydrochloric acid (*d* 1·18).

To obtain a separation of nickel, manganese, cobalt, and zinc (Fig. 6; Strip I) a solution of the metals in dilute hydrochloric acid was spotted on to a paper strip and allowed to dry in air. The solvent consisted of acetone containing 5% (v/v) of water to which was added 8% (v/v) of hydrochloric acid (*d* 1·18). A solvent movement of about 25 cm. was allowed in an atmosphere saturated with respect to the solvent. The solvent was allowed to evaporate and the strip exposed to ammonia vapour and then sprayed with a mixture of alizarin, rubeanic acid, and salicylaldoxime in alcohol. Nickel was detected as a blue band which had just moved from the original spot. Manganese formed a brownish band below the nickel, whereas cobalt formed a brown band below manganese and zinc was in the solvent front. Approximate R_F values were : Ni, 0·07, Mn 0·3, Co 0·6, Zn 0·9.

The separation of nickel, manganese, cobalt, copper, and iron by using a mixture of methyl propyl ketone, acetone, and hydrochloric acid has been reported by Arden *et al.* (*loc. cit.*), and the application of this separation to the quantitative estimation of these metals will be described in another paper.

(e) *Analytical Group IV* : Ca, Sr, *and* Ba.—*Recommended method.* The metals are present as chlorides, and the solvent used is pyridine containing 20% (v/v) of water and 1% (w/v) of potassium thiocyanate.

This mixture of metals has not proved easy to separate. The use of solvents alone or containing water or acid was not effective with the chlorides or nitrates. With potassium thiocyanate in certain solvents some success was achieved, and of these solvents pyridine containing 10—20% of water (and 0·5—1·0% of thiocyanate) proved the best. An aqueous solution of the alkaline-earth metals as chlorides was spotted on the paper strip and allowed to dry in air. Extraction was allowed to proceed for 5—6 hours which gave a run of about 20 cm. The atmosphere in the cylinder was saturated with respect to pyridine, and the relative humidity was also controlled between 65 and 80% by having at the bottom of the cylinder a beaker containing either saturated ammonium nitrate or ammonium chloride solution. After the paper had been dried, the separated salts were developed with alizarin to identify the calcium and with sodium rhodizonate to reveal barium and strontium. The calcium occurred just behind the solvent front, with the strontium a little way above the calcium (Fig. 6; Strip II). Under the best conditions the movement of barium is slight, but in some cases, particularly on warmer days if the temperature is not controlled, there is a tendency for the barium to move downwards towards the strontium. This movement is often irregular and appears to be connected with the movement of the strontium, for it decreases or stops once the calcium and strontium are separated from the barium.

(f) *Analytical Group V*: Li, Na, *and* K. *Recommended method.* The metals are present as their chlorides in neutral solution and the solvent used is methyl alcohol.

Only preliminary work has been carried out on the separation of the alkali metals and so far only lithium, sodium, and potassium have been examined. With an aqueous solution containing 100 μg. of each of the metals as chlorides, in 0·05 ml. of solution, separations were obtained with methyl alcohol as solvent. The position of the alkali-metal bands was found by spraying with a mixed solution of silver nitrate and fluorescein and then drying the strip. Three chloride bands were detected, lithium some distance behind the solvent front, sodium about half-way between the original position and the solvent front, and the potassium band just below the original position.

(g) *The Platinum Metals*: Pt, Pd, Rh, Ir, Ru, Os, *and* Au.—*Recommended method.* The metals are present as their chlorides or sodium chloro-salts and the solvent used is methyl ethyl ketone containing 30% (v/v) of hydrochloric acid (*d* 1·18).

Several methods of separation of the platinum metals have been achieved depending on the solvent used and on the valency states of the metals in solution. In order to maintain standard conditions, a chloride solution was prepared by fusing gold, palladium, platinum, rhodium, and iridium chlorides with sodium peroxide. A second mixture also included ruthenium and osmium. The melt was dissolved in water and acidified with hydrochloric acid. The chloride solution was spotted on a paper strip and allowed to dry thoroughly in air. For the subsequent detection of the metals, stannous chloride was found to be a suitable developing reagent for platinum, palladium, gold, and rhodium. A more sensitive reagent was a mixture of stannous chloride and potassium iodide solutions. The strip was warmed gently for the full development of the rhodium colour. Iridium was reduced to the colourless trichloride by stannous chloride. A good spot test was not found for iridium, but reoxidation to the brown tetrachloride was found to be fairly satisfactory. A solution of thiourea in 5N-hydrochloric acid was used to test for ruthenium and osmium, and the strip was warmed to develop the colours fully. The work has been mainly directed to the separation of gold, platinum, palladium, iridium, and rhodium and only a small number of experiments have included ruthenium and osmium. A number of solvents separated gold, platinum, iridium, and osmium from rhodium provided that the rhodium was present as sodium chlororhodite (Na_3RhCl_6); rhodium chloride ($RhCl_3$) is soluble in a number of organic solvents. Acetone +5% of hydrochloric acid (*d* 1·18) has been found particularly satisfactory provided that the ketone is dry and freshly distilled. The rhodium was left in the original spot, and gold, platinum, palladium, iridium, and osmium were obtained in overlapping bands, gold being in the solvent front. If, in the absence of gold, the original solution was reduced with sulphur dioxide, platinum, palladium, and osmium were still extracted from rhodium with acetone +5% (v/v) of hydrochloric acid (*d* 1·18) but iridium and ruthenium then remained with the rhodium.

Iridium tetrachloride moved together with the platinum band with all the solvents investigated, but in the presence of an organic solvent containing hydrochloric acid the tetrachloride was reduced or partly reduced to the trichloride. Iridium trichloride behaved similarly to sodium chlororhodite. This reduction of Ir^{IV} to Ir^{III} increased as the concentration of hydrochloric acid in the organic solvent increased. With acetone containing 5% (v/v) of hydrochloric acid (*d* 1·18) the extraction of iridium tetrachloride from rhodium was practically complete with little or no reduction to the trichloride. The presence of an oxidising agent such as sodium chlorate further aided the extraction by preventing reduction. Ruthenium was extracted by acetone +5% (v/v) of hydrochloric acid (*d* 1·18) as a wide diffuse band stretching from solvent front to original spot. If sulphur dioxide was first passed through the ruthenium chloride solution, the resulting solution was not extracted by the acetone solvent but remained with rhodium and tervalent iridium. The reduction of the chloride solution of the mixed platinum metals with sulphur dioxide first gave a clear solution, but in a short time a precipitate was formed. This deposit was shown to be due to insoluble ruthenium and osmium compounds. The reduced solution of platinum, palladium, and iridium chlorides was stable.

The separation of rhodium, iridium, platinum, palladium, and gold into four bands, one of which contained both rhodium and iridium, using methyl propyl ketone +30% (v/v) of hydrochloric acid (*d* 1·18) has already been reported (Burstall *et al.*, *loc. cit.*). The separation of silver, copper, palladium, platinum, and gold by using butyl alcohol saturated with N-hydrochloric acid has also been recorded by Lederer (*Nature*, 1948, **162**, 776). Methyl ethyl ketone containing 30% (v/v) of hydrochloric acid (*d* 1·18) has been used in place of methyl propyl ketone with satisfactory results (Fig. 6; Strip III). Either of the ketonic solvents rapidly reduced Ir^{IV} to the comparatively immobile Ir^{III} which moved with rhodium. With less than 30% (v/v) of hydrochloric acid (*d* 1·18) in methyl ethyl ketone, Ir^{IV} was partly extracted from the rhodium band owing to incomplete reduction. With methyl propyl ketone containing less than 30% (v/v) of hydrochloric acid (*d* 1·18) double bands of platinum were formed. On addition of ruthenium and osmium to the system, ruthenium was found with the rhodium and iridium, while osmium was found between, but not completely separated from, the gold and the platinum. The behaviour of ruthenium and osmium was similar with both ketonic solvents.

A number of R_F values were measured and shown to be fairly constant (Table V) providing conditions were sufficiently standardised. The solvent was prepared by dissolving 30 ml. of concentrated "AnalaR" hydrochloric acid (*d* 1·18) in 70 ml. of methyl propyl ketone or methyl ethyl ketone and the atmosphere of the separation vessel was saturated with respect to the solvent. The solution of platinum metals in 2N-hydrochloric acid was spotted on a paper strip and dried for 1 hour.

The solvent was freshly made up each day, since, when kept for a long time with acid, both ketones undergo some decomposition and darkening. The normality of the concentrated hydrochloric acid is likely to vary, but this will not affect the separation although some alteration in R_F values will be observed.

For the separation of rhodium and iridium after removal of gold, platinum, and palladium with either ketonic solvent, the test was run first with methyl propyl ketone or methyl ethyl ketone +30% (v/v) of hydrochloric acid (*d* 1·18), the solvent was allowed to evaporate, and the strip then sprayed with an oxidising agent, *e.g.*, chlorine water. After drying, the strip was re-run with acetone containing 5% (v/v) of hydrochloric acid (*d* 1·18). This second extraction removed the iridium in the new solvent front, which was then allowed to move to a point between the rhodium and palladium bands.

A number of other solvents have been found to give successful or partly successful separations. "Carbitol" or "Cellosolve" containing 20% (v/v) of hydrochloric acid (*d* 1·18) gave a separation of gold, platinum, palladium, and rhodium into 4 bands; "Cellosolve acetate" containing hydrochloric acid (*d* 1·18) gave similar results, but in all three cases quadrivalent iridium was found with the palladium band.

A graduated series of results was obtained on using the alcohols with 20% (v/v) of hydrochloric acid (*d* 1·18). These mixtures being used, the separation improved on ascending the series, methyl, ethyl, butyl, amyl. With amyl alcohol, separation of gold, platinum, palladium, and rhodium into four bands was obtained, but the platinum and palladium bands remained in contact. Iridium was reduced by the amyl alcohol solvent as already described for the ketonic solvents. With butyl alcohol saturated with 2N-hydrochloric acid a good separation of rhodium, platinum, palladium, and gold was obtained but iridium was found in a disperse band stretching from the gold to palladium.

(h) *Separation of Gold from the Platinum Metals.—Recommended method.* The metals are present as their chlorides, and the solvent used is ethyl ether containing 2% (w/v) of dry hydrogen chloride and 7·5% (v/v) of dry methyl alcohol.

TABLE V.

R_F *Values of platinum metals.*

			R_F Values.						
Operator.	Solvent.	Time of run, hrs.	Au.	Os.	Pt.	Pd.	Rh and Ir.	Ru.	Wt. of each metal present, μg.
A	COMeEt + 30% HCl	16	0·91	—	0·76	0·56	0·06	—	50
"	"	16	0·91	—	0·78	0·56	0·05	—	25
"	"	8	0·95	0·92	0·84	0·61	0·09	0·09	50
"	"	8	0·97	0·93	0·84	0·60	0·09	0·08	25
B	"	16	0·95	—	0·84	0·64	0·17	—	50
"	"	16	0·97	—	0·85	0·65	0·17	—	25
"	"	8	0·97	—	0·83	0·65	0·16	—	50
"	"	8	0·97	—	0·82	0·62	0·15	—	25
A	COMePr + 30% HCl	16	0·91	—	0·75	0·53	0·11	—	50
"	"	16	0·92	—	0·75	0·52	0·10	—	25
"	"	8	0·96	0·89	0·81	0·56	0·11	0·07	50
"	"	8	0·96	0·91	0·81	0·56	0·11	0·07	25
B	"	8	0·98	—	0·80	0·57	0·17	—	50
"	"	8	0·98	—	0·80	0·57	0·15	—	25

A useful quick method for the detection of small amounts of gold in chloride solutions of the platinum metals has been discovered. The solvent consisted of ethyl ether containing 1—2% (w/v) of dry hydrogen chloride to which was added 7·5% (v/v) of dry methyl alcohol. This mixture extracted gold in a narrow band in the solvent front, while the platinum metals remained in the original spot (Fig. 6; Strip V). By using this solvent it was found possible to detect 1 μg. of gold in several hundred times the amount of each of the platinum metals.

Several practical difficulties have been observed. In experiments with pure gold chloride solution, it was found that when an aqueous solution was allowed to evaporate to dryness on filter-paper, some of the gold salt was reduced to the metal and was not subsequently extracted. A solution in fairly concentrated (>2N.) hydrochloric acid, however, could be evaporated to dryness on a paper strip without reduction to the metal and subsequent extraction was complete. With a 12-hour gap between the drying and running of a strip, partial reduction to gold occurred even with use of concentrated hydrochloric acid. In all work with solutions containing gold chloride, therefore, the original solution was made acid with hydrochloric acid and after being spotted on a paper strip was allowed to dry in air for 1 hour and then run with solvent. The methyl alcohol was added to the solvent in order to increase the efficiency of extraction, by decreasing the rate of movement of ether which was too fast for complete extraction of the gold chloride. Addition of too much methyl alcohol brought about partial reduction of the auric chloride. Increase in the concentration of dry hydrogen chloride in the solvent to 4% (w/v) also caused reduction, but variation in the concentration between 1 and 2% (w/v) was without effect. The test was run in an atmosphere of solvent vapour, but the extreme volatility of the solvent made constant atmospheric conditions difficult to maintain. A number of modifications and different solvents were tried in order to overcome this disadvantage, but either the platinum metals moved or the gold was extracted in a band which tailed badly. An example of a solvent which produced tailing was glacial acetic acid containing 4% (v/v) of hydrochloric acid.

(i) *Separation of Mercury from other Metals.* (With Miss M. N. JENKINS.)—*Recommended method.* The metals are present as their chlorides and the solvent used is methyl acetate containing 3% (v/v) of methyl alcohol and 10% (v/v) of water.

The separation of mercury by using tetrahydrosylvan as solvent has already been reported (Arden *et al.*, *loc. cit.*). Methyl acetate was found to be a suitable and more readily available solvent for the extraction of mercury as chloride from the following metals: lead, copper, bismuth, cadmium, arsenic, antimony, iron, aluminium, chromium, nickel, cobalt, manganese, and zinc. A number of other solvents including ethyl acetate and methyl propyl ketone also gave good results. Mercuric chloride is soluble in a large number of organic solvents but is exceptional in that the partition coefficient between most solvents and water falls off rapidly as the acidity of the aqueous layer is increased. Methyl acetate extracts mercuric chloride under widely differing conditions but the width of the mercury band and its position relative to the solvent front vary considerably with small changes. Mercury was extracted in a very narrow band in the solvent front by the following method.

The test solution, which should not contain more than 5% (v/v) of hydrochloric acid (*d* 1·18) and must have pH <2, was spotted on a paper strip and allowed to evaporate for 10—15 minutes. The solvent was methyl acetate with 10% (v/v) of water and 3% (v/v) of methyl alcohol or the constant-boiling mixture of methyl acetate and methyl alcohol with an added 7% (v/v) of water. The solvent was run in an atmosphere saturated with respect to the vapour of a saturated solution of methyl acetate in water and the temperature was kept constant at 22°. The solvent moved sufficiently far in 20—30 minutes to effect a complete separation. After the solvent had been allowed to evaporate, the strip was made alkaline by exposure to ammonia vapour and sprayed with an alcoholic solution of diphenylcarbazide; mercury was then indicated by a blue band in the solvent front. Two solvent phases were clearly distinguishable on the strip; an upper aqueous phase containing impurities, and a dry solvent phase with the mercury in the front edge. The extent to which water could usefully be added to the solvent was controlled by the behaviour of the upper wet phase. As the amount of water in the solvent was increased the extraction of mercury was improved, but if the amount of water added was increased beyond a definite limit, which varied with temperature, only one aqueous phase was obtained on the strip and all the metals present moved down to the solvent front. The amount of water permissible decreased with increase in temperature. The original spot was not allowed to dry over a prolonged period in order to avoid the formation of basic salt which retained the mercury. It was possible to detect with ease 1 μg. of mercury by this method in the presence of a large excess of other metals. Some interference in the extraction of mercury was noted with concentrations of copper in the test solution exceeding 10% (w/v) but the extraction was largely independent of the ratio of mercury to copper.

(j) *Separation of Selenium and Tellurium.* (With N. F. KEMBER.)—*Recommended method.* The metals are present in dilute nitric acid solution, and the solvent used is dry butyl alcohol containing 40% (v/v) of dry methyl alcohol.

The following method has been developed for the separation of selenium and tellurium. A solution of the elements as selenite and tellurite in dilute nitric acid was spotted on a paper strip and allowed to dry thoroughly in air. The strip was treated with a solvent consisting of a mixture of 60% (v/v) of dry butyl alcohol and 40% (v/v) of dry methyl alcohol, in an atmosphere saturated with respect to the solvent vapour and with a relative humidity maintained at 50%. The solvent was allowed to diffuse 8—10 cm. down the strip (approx. 2 hours). After evaporation of the solvent, the strip was developed by spraying with stannous chloride solution. The tellurium which had moved only slightly from the position of the test sample was indicated as a black band, whereas selenium formed an orange band half-way between the solvent front and the original spot position (Fig. 6; Strip VI). The lower limit of detection for selenium, with the normal 1″ wide strip and stannous chloride as developer, was 5 μg., but 1 μg. was detected in 1000 μg. of tellurium by using a triangular strip. This separation was also obtained with test solutions consisting of tellurate and selenate in dilute nitric acid, but more difficulty was experienced in detecting the position of the bands. Sulphate, if present, did not affect the separation but remained with the tellurium. The original spot on the paper strip had to be thoroughly dry, otherwise excessive tailing of tellurium occurred; moreover, both alcohols in the solvent mixture must be dry. Increase in the percentage of methyl alcohol in the solvent mixture gave more rapid extraction of selenium in a narrower band but excessive forward tailing of tellurium was also obtained. The humidity of the extraction vessel was controlled at approximately 50% by means of a saturated solution of calcium nitrate kept in the bottom of the container. Variation in the humidity was found to alter the extraction in the following ways: (*a*) Increase in humidity gave more complete extraction of selenium. (*b*) At relative humidities >30%, slight movement of tellurium took place; this increased as the humidity was raised. (*c*) The relative movement of selenium decreased as the humidity was increased. (*d*) "Edge effects" for selenium decreased as the humidity was raised.

The conditions chosen for extraction therefore represent a compromise.

(k) *Separation of Thorium, Scandium, and the Rare Earths.* (With N. F. KEMBER.)—*Recommended method.* The metals are present as nitrates, and the solvent used is tetrahydrosylvan containing 5% (v/v) of water and 10% (v/v) of nitric acid (*d* 1·42).

The separation of scandium from the rare earths on a column of cellulose by aid of an ethyl ether–nitric acid mixture has already been briefly reported (Burstall *et al.*, *loc. cit.*). A solvent containing diethyl ether is not suitable for use with the paper-strip technique, but tetrahydrosylvan was found to be a suitable solvent, after addition of water and nitric acid, for the separation of scandium and thorium from each other and from the rare earths, on the same strip.

A solution of the rare earths, thorium, and scandium in dilute nitric acid was spotted on a paper strip and dried thoroughly in air. The solvent, consisting of tetrahydrosylvan containing 5% (v/v) of water and 10% (v/v) of nitric acid (*d* 1·42), was allowed to diffuse about 15 cm. down the paper strip. By controlling the relative humidity of the atmosphere at about 80% with a saturated solution of ammonium chloride in the bottom of the extraction vessel, a narrow and concentrated band of scandium was obtained. The solvent was allowed to evaporate, and the strip placed for about 10 minutes in an atmosphere of ammonia. The strip was sprayed with an alcoholic solution of alizarin and finally with N-acetic acid; thorium was then detected as a violet-blue band with a sharp front edge about 0·6 cm. behind the solvent front. Scandium formed a more diffuse band about 2·5 cm. in front of the rare earths which moved only slightly from the original position of the test spot. With alizarin the rare earths gave a similar colour to thorium but a redder tint was obtained with scandium. By this method 1 μg. of scandium was detected in 1000 μg. of the rare earths.

Scandium was also separated from the rare earths by using methyl acetate containing 10% (v/v) of water and 5% (v/v) of nitric acid (*d* 1·42) as solvent. The strip was allowed a solvent run of 25 cm.; scandium was then found in a similar position to that obtained with tetrahydrosylvan but in a narrower band. Thorium, however, was detected as a more diffuse band between scandium and the solvent front.

(l) *Separation of* F, Cl, Br, *and* I. (With D. B. Rees Evans.)—*Recommended method.* The acid radicals are present as their sodium salts and the solvent used is pyridine containing 10% (v/v) of water.

The anions, fluoride, chloride, bromide, and iodide, have been separated as their sodium salts by using pyridine or acetone as solvent. The acetone used contained 20% (v/v) of water, and the pyridine was AnalaR pyridine, with 10% (v/v) of added water. Separations were not affected by a variation of ±2·5% in the water concentration of the solvents. The test solution, consisting of a neutral aqueous solution of sodium chloride, bromide, and iodide (the sodium salts were found preferable to the potassium salts), was spotted on a paper strip and allowed to dry in air. The strip was run in an atmosphere saturated with solvent vapour for 1½—2 hours. The solvent was allowed to evaporate from the strip which was then sprayed with a mixture of silver nitrate and fluorescein solutions. On drying, the halides appeared as three characteristic dark bands, which when viewed under ultra-violet light appeared as dark areas on a fluorescent background (Fig. 6; Strip IV). Strips one inch wide being used, it was possible to detect 1 μg. of bromide and 4 μg. of chloride or iodide in 0·05 ml. of original solution by this method. With a triangular strip, 1 μg. of chloride or iodide per 0·05 ml. of test solution was detected. Separations were carried out in which 1—10 μg. of one or two of the halides have been detected in the presence of 10 times the quantity of either one or both of the others. No difficulty has been experienced in dealing with concentrations up to 200 μg./0·05 ml. of each of the halides.

A more limited study has been made of the behaviour of fluoride. Sodium fluoride was added to the original solution of sodium chloride, bromide, and iodide. Strips were run with both the acetone and the pyridine solvent. The position of the fluoride band was detected by spraying with zirconium–alizarin reagent. For this purpose each strip was cut in two longitudinally; one part was then sprayed with silver nitrate–fluorescein reagent and the other with zirconium–alizarin solution. When pyridine was used as solvent the fluoride remained in the original spot. With the acetone solvent the fluoride moved but still remained separated from the chloride band. With this solvent a trace of fluoride was left in the original spot. Use of a wet spot overcame this disadvantage but R_F values were not then repeatable. R_F Values obtained by using a dry spot were fairly constant with both solvents as indicated below:

R_F *Values for halides.*

Radical.	Acetone + 20% (v/v) H_2O.				Pyridine + 10% (v/v) H_2O.			
Fluoride	—	—	0·26	0·24	—	—	0·00	0·00
Chloride	0·50	0·53	0·51	0·49	0·25	0·22	0·23	0·24
Bromide	0·62	0·62	0·62	0·60	0·47	0·47	0·47	0·47
Iodide	0·77	0·77	0·77	0·76	0·72	0·70	0·72	0·71

(m) *Miscellaneous Separations.* (With N. F. Kember.)—In addition to readily recognised groups of metals the separation of a number of special mixtures of metals has been examined, as follows: (1) The separation of nickel, manganese, cobalt, copper, and iron (of interest in analysis of steel) has been studied, the solvent being either acetone or methyl ethyl ketone mixtures with hydrochloric acid. (2) In parallel experiments, using the same solvents, the separation of uranium, vanadium, and titanium has been explored.

For this purpose two solutions were prepared, one containing nickel, manganese, cobalt, copper, and iron in dilute hydrochloric acid, and another containing uranium, vanadium, and titanium, also in dilute hydrochloric acid. A portion of each solution was placed upon a separate paper strip and allowed to dry in air; the solvent was then allowed to run down both strips for a distance of 15 cm. A series of approximate R_F values obtained with different solvents are shown in Table VI. It can be seen that nickel, manganese, cobalt, copper, and iron have been separated with methyl ethyl ketone +8% (v/v) of hydrochloric acid (*d* 1·18), and uranium has been extracted from vanadium and titanium with a variety of solvents.

Two lines drawn between a pair of R_F values in the table indicate that the two metals concerned are in bands which overlap. One line indicates that the bands just touch. The abbreviations D or VD written after an R_F value indicate that the band is diffuse or very diffuse. Where two R_F values are given for the same metal then the metal is in a double band.

With methyl ethyl ketone as solvent two phases were obtained on the paper strip; acetone, although miscible with water, also gave two phases. With both solvents the phases consisted of a lower dry solvent phase, in which the acid concentration was low, and an upper phase of aqueous solvent in which there appeared to be an acidity gradient, the strip being most acid at the top and becoming progressively less acid nearer the solvent front. The approximate position of the interphase boundary was measured and the R_F value is recorded with those of the metals in Table VI. It appears to be directly related to the proportion of acid and water in the solvent, the ratio of the wet to dry solvent phase increasing as the concentration of acid is increased and falling off as the water content is increased. The position of the interphase boundary is important in that copper tends to split into two bands, a main band in the wet solvent phase and a weaker band in the dry solvent phase. If, however, the R_F value of the interphase boundary is sufficiently high, copper is found only in the wet solvent phase. The behaviour of uranium is also unusual in that it is sometimes found in the wet solvent phase and at others in the dry solvent phase.

During a study of the double band formation of copper it was noticed that the acid ketonic solvents used extracted a certain amount of copper and iron from the filter-paper. After runs on blank sheets and strips of paper, a band of iron was detected in the solvent front and some way behind a band of copper was obtained. Further investigations are being made to extract this soluble inorganic material without interfering with subsequent chromatographic separations.

TABLE VI.

R_F *values with different solvents.*

Solvent. / Metal.	COMe$_2$ +5% (v/v) H$_2$O + 5% (v/v) HCl.	COMe$_2$ +10% (v/v) H$_2$O +5% (v/v) HCl.	COMeEt +6% (v/v) HCl.	COMeEt +8% (v/v) HCl.	COMeEt +5% (v/v) H$_2$O + 8% (v/v) HCl.	COMeEt +10% (v/v) H$_2$O + 10% (v/v) HCl.	COMeEt +10% (v/v) H$_2$O + 5% (v/v) HCl.
				Strip 1.			
Ni	0·09	0·12	0·01	0·01	0·01	0·10	0·005
Mn	0·21	0·20	0·13	0·18	0·13	0·13	0·01
Co	0·43	0·27	0·42D	0·54	0·30	0·21	0·04
Cu	0·61, 0·80	0·63, 0·92	0·65VD	0·71	0·72VD	0·53, 0·70D	0·26, 0·39
Fe	0·97	0·97	0·90	0·93	0·91	0·90	0·70VD
				Strip 2.			
Ti	—	0·17	—	—	—	0·10	0·02
V	0·18	0·17	0·07	0·14	0·09	0·12	0·03
U	0·65	0·81	0·76	0·87	0·73	0·62	0·30
R_F value of interface...	0·64	0·64	0·50	0·82	0·72	0·64	0·37

(3) *Separations with Butyl Alcohol.*—The solvent butyl alcohol saturated with 3N-hydrochloric acid, used for the separation of the metals of the analytical group IIa, has been employed in a number of other separations. The members of the following pairs of metals are mutually interfering, when undergoing estimation on the polarograph: copper and bismuth, vanadium and iron, uranium and molybdenum, and lead and antimony; but, as may be deduced from the R_F values in the table below, separation is possible by using butyl alcohol saturated with 3N-hydrochloric acid. A chloride solution of the metals is treated as described in Section (a) (p. 518). After suitable development, copper, vanadium, uranium, and lead are found on the top portion of the strip, above the iron band below which the bismuth, molybdenum, and antimony bands are located. The individual members of each of these groups of four metals may then be estimated by the polarograph since the other three metals present will not interfere.

R_F *Values with butyl alcohol* + 3N-*hydrochloric acid.*

Metal	V	Cu	Pb	U	Fe	Mo	Bi	Sb
R_F value	0·18	0·19	0·23	0·26	0·42	0·53	0·57	0·78

Enhanced Colours.—It has been noticed that when a strip is sprayed with developing reagent before all the solvent has evaporated, the colours obtained are often very much more intense, than those obtained normally with the reagent and the radical after solvent has been removed, *e.g.*, arsenic, antimony, and tin with dithizone in chloroform in the presence of ethyl acetoacetate, scandium and the rare earths with alizarin in the presence of methyl acetate, gold and the platinum metals with stannous chloride in the presence of various "Carbitol" derivatives, the halides with silver nitrate and fluorescein in the presence of pyridine.

It is thought that this effect may have application in increasing the sensitivity of "spot" tests. The opposite effect has also been noticed. It is then often necessary to warm the strip for some time after developing it to allow the colour reaction to proceed.

Preparation of Solvents.—*Acetone.* Refluxed with solid potassium hydroxide and permanganate for 1 hour; the fraction, b. p. 56° ± 0·5°, was used.

Methyl ethyl ketone. As acetone. The fraction, b. p. 79·5—79·7°, was used.

Methyl n-*propyl ketone.* As acetone. The fraction, b. p. 99—102°, was used.

Methyl alcohol. Redistilled, b. p. 63°.

n-*Butyl alcohol.* Dried over calcium; b. p. 116·5—117·5°.

Amyl alcohol and pyridine. Both of AnalaR brand.

Ethyl acetate. Shaken with saturated calcium chloride solution, dried ($CaCl_2$), and distilled; b. p. 76·5—77·5°.

Methyl acetate. Either the constant-boiling mixture with methyl alcohol, b. p. 54°, was used, or the ester was dried ($CaCl_2$) and distilled, the fraction of b. p. 56·5—58° being used.

Ethyl ether. Refluxed with alkaline permanganate, distilled, dried ($CaCl_2$), and fractionated. The solvent used was free from peroxide and had a water content of less than 1%.

Tetrahydrosylvan. As ethyl ether; the fraction of b. p. 79—80° was used.

DISCUSSION.

Measurement of R_F *Values.*—The method used for measuring R_F values requires explanation. The original solution was placed along a pencilled line ruled across the paper strip. The distance moved by an element was considered to be the distance between this line and the "centre of gravity" of the band formed by the element; this was compared with the movement of the solvent measured from the same line. This method of measurement was simple but suffered from several disadvantages; no indication was given of the width of a band, without which an R_F value can be misleading, *e.g.*, using amyl alcohol as solvent the R_F values for cadmium and mercury were very close but the bands were so narrow that separation occurred, whereas with the same amounts of lead and copper and the same solvent, a difference in R_F values was obtained, but without separation, the lead forming a narrow band in the forward area of a wide copper band. An alternative method of measurement would be to give the R_F values for the front and the rear boundary of each band; this, however, would be difficult for those bands with diffuse boundaries. When two liquid phases are obtained on a paper strip there is some advantage to be gained from using the aqueous phase front (Lederer, *Nature*, 1948, **162**, 776) as a reference point for the calculation of R_F values, but in many cases the position of the phase front has been very indeterminate and in others only one phase appeared to exist.

Constancy of R_F *Values.*—Providing close control of all the variables is maintained, constant R_F values are obtained. The necessity for such close control would be a disadvantage in routine applications but, as found with amino-acids (Consden *et al.*, *loc. cit.*), relative rates of movement are constant with less control. Thus, one band on a strip can usually be identified by its position relative to known bands. Again, the large number of characteristic "spot" tests available for the detection of inorganic radicals diminishes the necessity for accurate measurement of R_F values. Constancy of solvents, temperature, and saturation of the atmosphere being assumed, a number of factors were found to affect R_F values, *viz.*:

(*a*) The presence of other anions. This is very common. A good example is the presence of chloride in separations carried out with nitrate solutions.

(*b*) The acidity of the original solution. This effect has been reported by Lacourt *et al.* (*loc. cit.*), and variations have been found although the original solution was first allowed to evaporate. The cause may be due to the need for acid in the formation of a complex soluble in the organic solvent complex, *e.g.*, gold chloride. On the other hand, the presence of acid may tend to prevent complex formation, *e.g.*, the extraction of mercury with methyl acetate from a strongly acid solution.

(*c*) The time of running of a strip. This factor is not important in all cases but is important in certain separations. In the separation of copper, lead, bismuth, cadmium, and mercury with butyl alcohol saturated with 3N-hydrochloric acid, R_F values increase with the time of running and this coincides with a decrease in the rate of movement of the solvent front. The reason for these changes is not known with certainty but several points may be relevant. At the beginning of a run, the paper is in equilibrium with the prevailing laboratory atmospheric conditions but after some twelve or more hours in an atmosphere saturated with respect to butyl alcohol and dilute hydrochloric acid the strip has absorbed so much water vapour that difficulty is often found in detecting the exact position of the solvent front. It is this increase in water content of the cellulose which undoubtedly accounts for the decrease in the rate of movement of the solvent front. A further variable which has not, so far, been investigated is the esterification of the butyl alcohol.

(*d*) The presence and concentration of other cations. A few cases of interference by one metal on the extraction of another have been observed. This appears to be due to complex-cation formation or to the amphoteric properties of one of the metals.

The Formation of Two Phases.—The following explanation is put forward to correlate all the facts observed. Consider a solvent containing water passing down a strip of paper. The cellulose will absorb water from the solvent until an equilibrium is set up. Since the affinity of cellulose for water is much higher than that of most organic solvents, equilibrium is reached when the solvent is almost dry and the cellulose almost saturated with water. This will result in a clearly defined wet area of strip, and further down the strip there is an area of dry solvent. If now the percentage of water in the solvent is progressively increased, the ratio of area of wet phase to area of dry phase increases. This type of behaviour was observed on adding increasing quantities of water to the constant-boiling mixture of methyl acetate and methyl alcohol used for the extraction of mercury.

A solvent containing hydrochloric acid as well as water may next be considered. In some cases the presence of hydrochloric acid in the solvent increases its affinity for water. At the same time there is partition of hydrochloric acid between the water in the cellulose and the solvent. The net result is that the solvent competes more effectively with the cellulose for the water and travels further down the strip before losing all its water. This results in (1) a hydrochloric acid gradient in the wet part of the strip and a very low concentration of hydrochloric acid in the dry phase (both these effects can be noted in separations with acetone, hydrochloric acid, water mixtures); (2) a lower concentration of water in the wet phase area of the strip than that obtained when using an organic solvent containing water only; (3) a larger ratio of wet to dry phase on the strip. The last two points are supported by the behaviour of a number of solvents, *e.g.*, butyl alcohol, amyl alcohol, or methyl propyl ketone, with increasing hydrochloric acid content. The concentration of water in the paper underlying the wet phase decreases with increase of hydrochloric acid concentration until it is very difficult to detect the exact position of the interphase boundary. This change is accompanied by an increase in wet/dry phase ratio which continues until only one phase is obtained. These observations are illustrated by the behaviour of platinum on extraction with methyl propyl ketone containing hydrochloric acid.

Band Width.—Those salts which have a high solubility in organic solvents tend to be extracted in the solvent front. When this occurs, *e.g.*, mercuric chloride with methyl acetate, gold chloride with a mixture of ethyl ether and hydrochloric acid, and ferric chloride with acetone–hydrochloric acid mixtures, the width of the band in the solvent front is usually very much less than the width of the original spot. When two phases exist on a paper strip, a similar decrease in band width is sometimes noticed if a metal tends to travel just above the inter-phase boundary, *e.g.*, arsenious chloride with ethyl acetate–water mixtures. A somewhat different case arises when cadmium and mercury chlorides are extracted with butyl alcohol saturated with 3N-hydrochloric acid. Both form bands narrower than the original spot and neither is in the solvent front, although the cadmium is probably just above the interphase boundary. The second case is explicable if a soluble metallo-complex is formed only in the presence of a definite excess of water or acid concentration.

Further work is necessary to explain the other two cases.

It is hoped to devise more general separations when further basic knowledge of the behaviour of different salts with various solvents has been obtained.

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Chemical Research Laboratory,
Teddington, Middlesex.

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101. *Studies of Seed Mucilages. Part V. Examination of a Polysaccharide extracted from the Seeds of* Plantago ovata *Forsk by Hot Water.*

By R. A. Laidlaw and E. G. V. Percival.

Extraction of these seeds with hot water, after exhaustive extraction with cold water, yielded a polysaccharide fraction (PII, equiv., *ca.* 4000; uronic anhydride, *ca.* 3%; pentosan, *ca.* 90%; methylpentosan, nil). Hydrolysis of PII gave D-xylose (80%), L-arabinose (14%), D-galactose (a trace), an aldobiuronic acid (*ca.* 0·3%), and an insoluble residue (*ca.* 3%). Acetylation, deacetylation and methylation, and fractional precipitation gave products *A* (63%), *B* (32%), and C (5%). Methanolysis and hydrolysis of *A* gave trimethyl D-xylopyranose (8 parts), trimethyl L-arabofuranose (3 parts), tetramethyl D-galactopyranose (*ca.* 0·3%), a 2 : 6-dimethyl hexose (1 part), 2 : 4-dimethyl D-xylopyranose (4 parts), 3-methyl D-xylopyranose (8 parts), and D-xylopyranose (1 part).

In Part III (Laidlaw and Percival, *J.*, 1949, 1600) the polysaccharide obtained from *Plantago ovata* Forsk seeds by extraction with cold water (PI) was shown to be highly complex. The main constituents liberated on hydrolysis were D-xylose (46%), L-arabinose (7%), and 2-D-galacturonosido-L-rhamnose (40%), but after acetylation and methylation no uronic acid residues remained. Although it was possible to indicate the mode of linkage of the xylose and arabinose residues in the methylated polysaccharide, it was thought that at least two associated polysaccharides were present in the mucilage, a polyuronide and a neutral fraction. This indeed agreed with Anderson and Fireman's observation (*J. Biol. Chem.*, 1935, **109**, 437) that products containing variable quantities of uronic acid residues could be isolated depending on purely mechanical differences in the mode of extraction. To throw further light on the matter, we

have studied the properties of the polysaccharide (PII) obtained by extraction of the seeds with hot water after exhaustive extraction with cold water. The proportion of uronic acid residues in PII is much less than in PI, the equivalent by titration being *ca.* 4000 (cf. 700 for PI), and PII contains only 3% of uronic anhydride; the pentosan content is correspondingly higher (90%) and L-rhamnose is absent. The uronic anhydride is considered to arise from an associated [illegible]ronide. Hydrolysis of PII gave D-xylose (80%), L-arabinose (14%), a trace of galactose, and a small amount (0·3%) of a substance which appeared to be the barium salt of an aldobiuronic acid with properties different from that isolated from PI (*loc. cit.*).

Acetylation and methylation gave a methylated polysaccharide which was fractionated to give products *A*, *B*, and *C* (see table, p. 531). Products *A* and *B*, which together amounted to 95% of the methylated mucilage, appeared to be essentially similar, apart from the lower specific viscosity, and presumably, molecular weight of *B*.

Product *A*, on methanolysis afforded a mixture of methylated sugar glycosides which were separated by solvent extraction (Brown and Jones, *J.*, 1947, 1344) to give the four fractions discussed below, *viz.*, I (47·8%), II (15·7%), III (32·2%), and IV (4·4%). Fraction I was a mixture of trimethyl methyl-D-xylopyranosides and -L-arabofuranosides similar to that described previously (*loc. cit.*): crystalline trimethyl D-xylopyranose, its anilide, trimethyl D-xylopyranolactone, and 2 : 3 : 5-trimethyl L-arabonamide were isolated. From a consideration of the lactone equilibria it was estimated that trimethyl L-arabofuranose constituted about 14% of the products of hydrolysis of the methylated mucilage. Fraction II on hydrolysis and separation on a column of powdered cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) gave six fractions. Of these, fraction II(1) was identical with I; II(2) was tetramethyl D-galactopyranose; II(3) has not been identified although it appears to be a 2 : 6-dimethyl aldohexose; II(4) proved to be a mixture of 2 : 3-dimethyl and 2 : 4-dimethyl D-xylose. Complete methylation gave trimethyl D-xylopyranose as the sole product, and the mixed lactone obtained on oxidation, the equivalent weight of which by titration corresponded to a dimethyl pentonolactone, showed $[\alpha]_D^{17}$ +30·8° $\longrightarrow$ 45·2° (96 hours) corresponding to a mixture of 2 : 3-dimethyl D-xylofuranolactone (40%) and 2 : 4-dimethyl D-xylopyranolactone (60%). Oxidation of the mixed sodium salts with periodic acid (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1473) gave formaldehyde in amount corresponding to the presence of 38% of sodium 2 : 3-dimethyl xylonate, and the syrupy amide gave a negative Weerman test (*Rec. Trav. chim.*, 1917, **37**, 16). A crystalline anilide, m. p. 158°, obtained from fraction II(4) was identified as slightly impure 2 : 4-dimethyl D-xylose anilide.

Fraction II(5) crystallised completely to give 2 : 4-dimethyl β-D-xylose which was identified by the properties of its lactone, by the facts that the derived amide gave a negative Weerman test and yielded no formaldehyde on periodate oxidation, and by comparison with a standard on the paper chromatogram.

Fraction II(6) proved to be 3-methyl xylose.

Fraction II(3) has defied identification; a syrup having $[\alpha]_D$ −19°, it was readily oxidised by sodium hypoiodite and was thus an aldose. Oxidation gave a furanolactone {$[\alpha]_D$ −50° $\longrightarrow$ −33° (18 days)}, showing the hydroxyl group on $C_{(4)}$ to be free. The derived crystalline *amide*, which analysis showed to be a dimethylhexonamide, gave a negative Weerman test showing the presence of a methoxyl group on $C_{(2)}$. The R_G value (Hirst and Jones, *J.*, 1949, 928) of fraction II(3), 0·80, is higher than that for any dimethyl hexose recorded so far, but the brown colour formed with aniline oxalate was easily distinguishable from the pink colour given by pentose derivatives. Oxidation with periodic acid (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456) gave no acetaldehyde which, since the hydroxyl on $C_{(4)}$ is free, excludes all (except 5-substituted) 6-deoxyhexoses, in any event an unlikely possibility. No formaldehyde was released on oxidation with periodate (Reeves, *loc. cit.*) and this, coupled with the knowledge that the hydroxyl group on $C_{(4)}$ is free, makes it probable that a methoxyl group resides on $C_{(6)}$. That fraction II(3) was an individual substance appeared likely from the definition of the spot on the paper chromatogram and the isolation of a crystalline amide; complete methylation and hydrolysis gave a syrup which again gave a single spot on the chromatogram, although this observation would not exclude the presence of a mixture of D- and L-forms. The R_G value observed (0·96) for the last-mentioned product appears to exclude tetramethyl galactopyranose (R_G 0·88); this is confirmed by the failure to isolate a tetramethyl hexose anilide which also seems to remove the possibility of the parent sugar being mannose. The examination of the original hydrolysed PII on the paper chromatogram seems to exclude idose and talose as possibilities. Gulose on the other hand has the same R_G value as arabinose and would, therefore, escape detection, but gulose has not, so far, been isolated from a natural product.

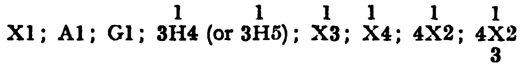
Fraction III on hydrolysis and fractionation on a cellulose column gave four fractions as follows: III(*a*) having R_G 0·7; III(*b*), III(*c*), and III(*d*), having R_G 0·39.

Fraction III(*a*) gave a syrupy lactone $\{[\alpha]_D^{18} +12° \longrightarrow +27°$ (50 hours)}, and the derived amide gave a negative Weerman reaction and a 20% yield of formaldehyde on periodate oxidation. Examination on the paper chromatogram showed III(*a*) to contain a mixture of 2 : 3-dimethyl and 2 : 4-dimethyl xylose, and from the above evidence the relative proportions were taken as 1 : 4. Faint traces of II(3) and of a monomethyl xylose were also present. Fraction III(*b*) crystallised to give 3-methyl D-xylose (80%), together with a syrup which, on oxidation, gave crystalline 3-methyl D-xylofuranolactone as the only product. Fraction III(*d*) gave the same crystalline lactone on suitable treatment, and III(*c*) gave crystalline 3-methyl xylose anilide. No 2-methyl xylose derivatives were detected, although they occurred in the products of hydrolysis of methylated PI (Part III, *loc. cit.*).

Fraction IV consisted almost entirely of methyl D-xylosides, chromatographic analysis of the hydrolysed syrup giving one spot only, corresponding to xylose, and the identity of D-xylose was confirmed as the crystalline dibenzylidene dimethylacetal (Breddy and Jones, *J.*, 1945, 738).

On the methanolysis of product *B* and separation by solvent extraction, five fractions were obtained which on qualitative examination by paper chromatography appeared closely similar to the fractions obtained from *A*, and no other individual sugars were present.

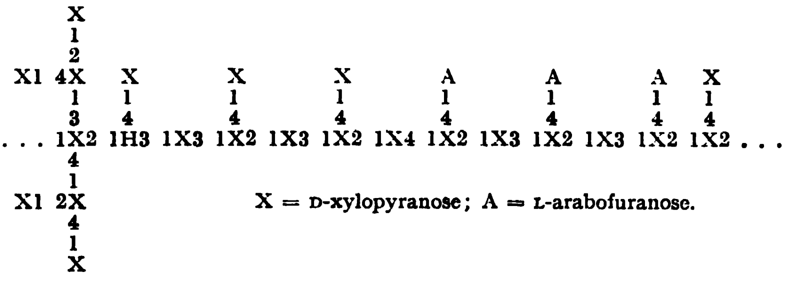
Allowing for the demethylation known to occur during methanolysis (Part III, *loc. cit.*) it was calculated that product *A* on hydrolysis gave trimethyl D-xylopyranose (8 parts), trimethyl L-arabofuranose (3 parts), tetramethyl D-galactopyranose (*ca.* 0·3%), 2 : 6-dimethyl hexose (1 part), 2 : 3-dimethyl D-xylopyranose (1 part), 2 : 4-dimethyl D-xylose (4 parts), 3-methyl D-xylopyranose (8 parts), and D-xylopyranose (1 part). Thus, in the polysaccharide the following units must be present, linked as shown :



$$\mathrm{X1;\ A1;\ G1;\ \overset{1}{3H4}\ (or\ \overset{1}{3H5});\ \overset{1}{X3};\ \overset{1}{X4};\ \overset{1}{4X2};\ \underset{3}{\overset{1}{4X2}}}$$

{X = D-xylopyranose; G = D-galactopyranose;
A = L-arabofuranose; H = hexose.}

No information is available at present to show how these units are related in the mucilage molecule. Thus, no definite structural formula can be assigned to the PII repeating unit, but the formula indicated below, one of many possible variants, would explain the properties of the methylated polysaccharide.


X
1
2
X1 4X X X X A A A X
1 1 1 1 1 1 1 1
3 4 4 4 4 4 4 4
. . . 1X2 1H3 1X3 1X2 1X3 1X2 1X4 1X2 1X3 1X2 1X3 1X2 1X2 . . .
4
1
X1 2X
4
1
X

X = D-xylopyranose; A = L-arabofuranose.

The galactose end-groups have been neglected in this formula, but it may be that in the mucilage molecule we have 13—14 such repeating units linked together and terminated by a D-galactopyranose residue.

Such a repeating unit should yield on oxidation with potassium periodate (Halsall, Hirst, and Jones, *J.*, 1947, 1427) 8 moles of formic acid, from the xylopyranose end-groups, *i.e.*, 0·00225 mol./g. The value found in practice for PII was 0·00234 mol./g., in good agreement with the theoretical figure. Further, a molecule of this constitution would use 20 moles of periodate or 0·00563 mol./g. The experimental figure (0·00535 mol./g. after 15 minutes when the initial rapid uptake appears to be complete) is in reasonable agreement. The higher figure (0·00674 mol./g.) obtained after 3 days may possibly be due to over-oxidation.

We may now compare the results from PII with those from PI. Methylated PI on hydrolysis yielded 2 : 3 : 4-trimethyl D-xylose (6 parts), 2 : 3 : 5-trimethyl L-arabinose (1 part), 2 : 4-dimethyl D-xylose (1 part), 3-methyl D-xylopyranose (4 parts), 2-methyl D-xylopyranose (1 part), and D-xylopyranose (2 parts). Thus, though we have in each case the same type of highly-branched structure considerable differences in detail are evident. Approximately the same proportion of end-groups is present in each case, but in PII the amount of arabinose derivatives is doubled at the expense of the xylose derivatives. Again, PII appears to contain a much higher proportion of doubly-linked xylose units; 1 : 4-linked D-xylose, present in PII, could not be identified in PI, though it was found in the mucilage from *P. lanceolata* (Percival and Willox, Part IV, *J.*, 1949, 1607). Further, neither 2-methyl xylose could be obtained from methylated PII, and the proportion of D-xylose units linked through four positions was much less than in PI. Finally, no methylated derivatives of D-galactose, nor the unknown hexose, obtained from PII, were isolated from PI. Thus, PI and PII are to be regarded as distinct polysaccharides; it may well be that each of these is in itself a mixture of closely-related polysaccharides, but there is no evidence that they could be mixtures of relatively simple xylans and arabans constituted from single sugar units. The relatively high yield of L-arabinose obtained on the hydrolysis of PII, its correspondence with the yield of trimethyl methylarabofuranosides obtained on methanolysis of the methylated polysaccharide, and the failure to detect any partly methylated L-arabinose derivatives in the hydrolysis of either methylated PI or methylated PII prove that the arabinose units occur as end groups as, for example, in gum arabic (Smith, *J.*, 1940, 1035) and are not derived from an associated araban.

EXPERIMENTAL.

Evaporations were conducted under diminished pressure unless otherwise stated. Temperatures are bath-temperatures. Fractions from the cellulose column were evaporated to dryness, dissolved in water, digested with charcoal, and filtered hot; the aqueous solution was then evaporated to dryness and exhaustively extracted with boiling acetone, and the extracts were evaporated to dryness.

Preparation of PII.—Product PI was removed from the seeds by extraction (Part III, *loc. cit.*), and the seeds were washed continuously with cold water until no more mucilage was removed. The residue was then extracted with hot water (90—95°), and the highly viscous solution separated by filtration through muslin. The filtrate, on cooling, set to a gel from which the mucilage was precipitated by the addition of acidified ethanol (4 volumes; 20 c.c. of concentrated hydrochloric acid per l.). The fibrous product was dried with ethanol and ether and in a vacuum over phosphoric oxide (Found: equiv., by titration, *ca.* 4000; uronic acid, *ca.* 3%; pentosan, 90%; methylpentosan, nil; ash, 1·41%, unchanged on treatment with sulphuric acid). Precipitation with ethanol alone yielded a product with 1·46% of ash (as sulphate, 1·83%).

Hydrolysis of PII with Oxalic Acid.—The dry mucilage (1·502 g.) was hydrolysed with oxalic acid (3%; 75 c.c.) at 100°. $[\alpha]_D^{16}$ was −11° (1 hour); +12·5° (2 hours); +25° (3 hours); +38° (6 hours); +40° (52 hours, constant). A larger quantity (46·92 g.) was hydrolysed as above for 6 hours. The insoluble residue (1·43 g.) was removed and the filtrate neutralised with barium carbonate, filtered, and evaporated to 200 c.c. This solution was filtered into ethanol (2 l.) to give a white barium salt (X) (0·19 g.). Evaporation of the alcoholic solution yielded a reducing syrup (S) (43·5 g.). The salt X showed Ba, 15·4% and $[\alpha]_D^{17}$ +39° in water (*c*, 1·0). Syrup S partly crystallised. Trituration of the mixture (22·47 g.) with glacial acetic acid gave D-xylose (7·02 g.) which, on recrystallisation from ethanol showed m. p. and mixed m. p. 140° and $[\alpha]_D^{17}$ +80° falling to +20° after 4 hours in water and yielded xylosazone, m. p. and mixed m. p. 157°. Evaporation of the acetic acid washings gave a syrup (S′) (15·46 g.), a portion of which was treated with phenylmethylhydrazine. No precipitate of galactose phenylmethylhydrazone was obtained.

Syrup S′, on treatment with diphenylhydrazine, yielded L-arabinose diphenylhydrazone, m. p. 194° not depressed on admixture with an authentic specimen, in an amount corresponding to the presence of 14·2% of anhydroarabinose in the mucilage.

Paper chromatographic investigations of S′ indicated the presence of xylose and arabinose along with a trace of galactose.

Acetylation.—The product PII (45 g.) was moistened with ethanol and dispersed with shaking in pyridine (750 c.c.), and acetic anhydride (500 c.c.) was added slowly with continuous stirring. The mixture was then heated at 100° for 3 hours and left at room temperature for a further 48 hours, whereafter the acetate was precipitated by pouring the mixture into water (10 l.) and washed thoroughly in running water till free from pyridine. Yield, 60 g. (Found : CH_3·CO, 30·9%). The properties of this material were unchanged on reacetylation.

Methylation.—The acetate was methylated directly in three 20-g. portions with methyl sulphate and sodium hydroxide as described in Part III (*loc. cit.*), each portion receiving four methylations. The products were combined and dissolved in chloroform, the solution was dried (Na_2SO_4), and the methylated polysaccharide fractionally precipitated by the addition of light petroleum (b. p. 40—60°), to give the fractions listed in the table.

Fraction.	Yield, g.	OMe, %.	$[\alpha]_D^{16}$ (CHCl$_3$).	$\eta_{sp.}^{20}/c'$.*
A	20·0	35·8	−121°	55·5
B	10·0	35·8	−120	19·3
C	1·6	27·1	−112	very low

* *c′* is the concentration in g.-mols. of methylated anhydroxylose residues per l.

Fraction *C* was obtained by evaporation of the residual solution almost to dryness and subsequent trituration with light petroleum. The properties of *A* and *B* were unchanged on further methylation. Neither *A* nor *B*, nor *C* contained any appreciable amount of uronic acid.

Hydrolysis of the Methylated Polysaccharide.—Fraction *A* (18·7 g.) was hydrolysed with methanolic hydrogen chloride (3%; 350 c.c.) for 21 hours at 80°. After neutralisation with silver carbonate, filtration, and evaporation, a non-reducing syrup (21·1 g.) was obtained.

Fractionation by Solvent Extraction.—The above syrup (20·4 g.) was dissolved in water (50 c.c.) and extracted with light petroleum (b. p. 38—40°) for 16 hours to give fraction I (9·725 g.), η_D^{17} 1·4423. Extraction with the same solvent for a further 210 hours gave fraction II (3·207 g.), η_D^{18} 1·4577. The residual aqueous solution was then extracted with chloroform for 20 hours to yield fraction III (6·571 g.), η_D^{16} 1·4722. Evaporation of the residue gave fraction IV (0·888 g.), η_D^{17} 1·4840. Recovery was 100%.

Hydrolysis and Fractionation of Fraction B.—Fraction B (9·1 g.) on methanolysis as above yielded a syrup (10·1 g.). Separation of the glycosides was again effected by solvent extraction. Thus, the syrup (8·95 g.) yielded, with light petroleum, fractions V (14 hours) (3·944 g.), η_D^{19} 1·4413, VI (+ 7 hours) (0·201 g.), η_D^{16} 1·4545, and VII (+90 hours) (0·745 g.), η_D^{12} 1·4580. Chloroform gave fraction VIII (17 hours) (2·655 g.), η_D^{16} 1·4675, and evaporation of the aqueous residue furnished fraction IX (1·375 g.), η_D^{19} 1·4683. Recovery was 8·920 g. (99·7%).

Examination of Fraction I.—Fraction I (9·04 g.) was hydrolysed with nitric acid (2%; 150 c.c.) at 100°. $[\alpha]_D^{17}$ were +19° (1 hour); +7° (3 hours); +4° (6 hours, constant). Neutralisation with barium carbonate, filtration, and evaporation of the filtrate left a residue which was exhaustively extracted with boiling acetone. The acetone extracts were combined and evaporated to yield a reducing syrup (6·97 g.). Several crops (total, 2·83 g.) of crystalline material were removed during a prolonged period, which on recrystallisation from ether gave trimethyl α-D-xylopyranose, m. p. and mixed m. p. 92°, $[\alpha]_D^{17}$ +63° (2 minutes), +33° (30 minutes), +19° (2 hours, constant) (*c*, 1·43 in water) (Found: C, 50·2; H, 8·1; OMe, 47·9. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·4; OMe, 48·4%). With alcoholic aniline the characteristic trimethyl D-xylose anilide was obtained (Part III, *loc. cit.*), m. p. and mixed m. p. 98° and $[\alpha]_D^{17}$ −84° (4 minutes), −70° (45 minutes), −44° (90 minutes), +34° (345 minutes), +47° (24 hours, constant) (*c*, 0·32 in ethanol). The residual syrup (3·48 g.) was examined on the paper chromatogram which indicated the presence of trimethyl xylose and/or trimethyl arabinose, along with traces of other components.

Attempted Separation on a Column of Cellulose.—The residual syrup (cf. preceding paragraph) (3·40 g.) was fractionated on a column of cellulose (15″ × 1·2″) (Hough, Jones, and Wadman, *loc. cit.*), the eluent being light petroleum (b. p. 100—120°)-butanol (7 : 3) saturated with water. Four main fractions were collected: (i) 1·00 g., $[\alpha]_D^{17}$ −10° (*c* 2·67 in water); (ii) 1·13 g., $[\alpha]_D^{17}$ −11° (*c*, 3·25 in water); (iii) 0·55 g., $[\alpha]_D^{17}$ −5° (*c*, 1·57 in water) (these three gave spots on the paper chromatogram corresponding to trimethyl xylose and/or trimethyl arabinose); (iv) 0·27 g., obviously composed of less fully methylated materials. Recovery was 2·95 g. (87%). Syrups (i), (ii), and (iii) were recombined (2·30 g.), dissolved in water, and oxidised at room temperature with bromine till non-reducing (4 days). After treatment with silver carbonate and hydrogen sulphide, evaporation gave a syrupy product which was fractionally distilled to give (*a*) 1·06 g., b. p. 95—105°/0·01 mm., η_D^{18} 1·4496 (Found: OMe, 48·4. Calc. for $C_8H_{14}O_5$: OMe, 48·9%), and (*b*) 0·82 g., b. p. 105—125°, η_D^{18} 1·4551 (Found: OMe, 47·6%). Portion (*a*) showed $[\alpha]_D^{17}$ −25° (5 minutes), −24° (1 hour), −21° (31 hours), −14° (100 hours), −11° (200 hours), −10° (318 hours, constant) (*c*, 3·14 in water). Portion (*a*) (62·8 mg.) required 5·50 c.c. of 0·0565N-sodium hydroxide for neutralisation to phenolphthalein (Calc. for $C_8H_{14}O_5$: 5·84 c.c.) and on treatment with methanolic ammonia yielded crystalline 2 : 3 : 5-trimethyl L-arabonamide. On recrystallisation (ethyl acetate) this showed m. p. and mixed m. p. 136° and $[\alpha]_D^{17}$ +21° (*c*, 1·41 in water) (Found: C, 46·0; H, 8·05; N, 6·95; OMe, 43·7. Calc. for $C_8H_{17}O_5N$: C, 46·3; H, 8·3; N, 6·8; OMe, 44·9%). Portion (*b*) showed $[\alpha]_D^{17}$ −9° (5 minutes), −8° (4 hours), −4° (29 hours), +3° (100 hours), +6° (200 hours, constant) (*c*, 3·451 in water); 34·5 mg. required 2·95 c.c. of 0·0565N-sodium hydroxide for neutralisation (Calc. for $C_8H_{14}O_5$: 3·21 c.c.). It gave a syrupy amide, $[\alpha]_D^{16}$ +35° (*c*, 2·94 in water). Portion (*b*) partly crystallised when kept, to yield 2 : 3 : 4-trimethyl xylopyranolactone, m. p. and mixed m. p. 50° (Found: C, 50·6; H, 7·5; OMe, 48·1. Calc. for $C_8H_{14}O_5$: C, 50·6; H, 7·4; OMe, 48·9%).

Examination of Fraction II.—Fraction II (3·20 g.) was hydrolysed with nitric acid (2%; 100 c.c.) at 100°: $[\alpha]_D^{17}$ +28° (1 hour); +22° (2 hours); +16° (4 hours); +14° (6 hours, constant). Appropriate treatment gave a reducing syrup (2·65 g.). This syrup (2·5 g.) was combined with column-fraction (iv) from fraction I above, and fractionation effected on a column of cellulose (27″ × 1·2″) as before. This gave: (1) 0·11 g., R_G 0·94, (2) 0·065 g. (0·88), (3) 0·56 g. (0·80), (4) 0·69 g. (0·74), and (5) 0·59 g. (0·66); a further fraction, (6) 0·14 g. (0·39), was obtained by washing the column with water. Recovery was 2·16 g. (76·4%).

Fraction (1). This corresponded to fraction I.

Fraction (2). On treatment with alcoholic aniline this yielded 2 : 3 : 4 : 6-tetramethyl D-galactose anilide, m. p. 189°, not depressed on admixture with an authentic specimen (Found: OMe, 39·1. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·9%).

Fraction (3). The syrup showed OMe, 33·6% and $[\alpha]_D^{17}$ −19° (*c* 1·35 in water). On the paper chromatogram it gave a brown spot when sprayed with aqueous aniline oxalate and heated. Oxidation was easily effected with alkaline hypoiodite under standard conditions (Found: *M*, 180. Calc. for $C_8H_{16}O_6$: *M*, 208). A test oxidation on D-glucose gave *M*, 180 (Calc. for $C_6H_{12}O_6$: *M*, 180). Fraction (3) failed to form a crystalline anilide.

The syrup (3) (0·118) was kept at 80° with 1% methanolic hydrogen chloride. $[\alpha]_D^{17}$ was −75° (40 minutes) and −82° (230 minutes, constant).

Methylation.—Neutralisation with silver carbonate, filtration, and evaporation yielded a non-reducing syrup which was methylated 3 times with the Purdie reagents, and the highly mobile syrupy product distilled at 80°/0·01 mm. The distillate (43 mg.; OMe, 58·1%) was hydrolysed with nitric acid (2%; 10 c.c.) at 100°. $[\alpha]_D^{17}$ was −64° (zero time), −41° (50 minutes), −34° (2 hours, constant) (Calc. as methylglycosides). Appropriate treatment gave the free sugar as a syrup (20 mg.) which failed to crystallise. On investigation by means of the paper chromatogram this showed one spot only at R_G 0·96. No crystalline anilide could be obtained.

Lactone Formation.—Fraction (3) (0·11 g.) was converted into the lactone. The product (70 mg.)

did not crystallise (Found: OMe, 32·8%). $[\alpha]_D^{18}$ was −50° (10 minutes), −46° (95 hours), −36° (263 hours), −33° (432 hours, constant) (*c*, 0·606 in water). The lactone (9·1 mg.) required 2·08 c.c. of 0·0249N-sodium hydroxide for neutralisation (Calc. for $C_8H_{16}O_5$: 1·80 c.c.).

Amide Formation.—The above lactone was reclaimed from polarimetric solution by evaporation and redistillation. A portion of this material (50 mg.) was converted into the amide. A white crystalline solid was obtained, which on recrystallisation (ethyl acetate) had m. p. 131—132° and gave a negative Weerman test (Found: C, 42·9; H, 7·7; N, 6·8; OMe, 30·0. Calc. for $C_8H_{17}O_6N$: C, 43·0; H, 7·7; N, 6·3; OMe, 27·8%).

Periodate Oxidations.—The free sugar (15·2 mg.) was oxidised according to the method of Nicolet and Shinn (*loc. cit.*). No acetaldehyde was detected, whereas L-rhamnose (16·0 mg.) gave acetaldehyde in 90% yield.

Fraction (3) (19·0 mg.) was oxidised according to the method of Reeves (*loc. cit.*), but no formaldehyde was produced. A sample of D-xylose (17·0 mg.) under the same conditions yielded the formaldehyde–dimedon compound (12·5 mg.), m. p. and mixed m. p. 187°.

Fraction (4).—This was a syrup which showed $[\alpha]_D^{18}$ +16° (*c*, 3·85 in water) and OMe, 33·7%. On the paper chromatogram a pink colour was obtained on spraying of the spot with aniline oxalate and heating.

Anilide Formation.—Treatment of the syrupy fraction (4) (20 mg.) with alcoholic aniline gave a crystalline product, which, on recrystallisation (acetone–ether–light petroleum) had m. p. 158°, mixed m. p. with 2 : 3-dimethyl D-xylose anilide, 128° (Found: OMe, 28·0. Calc. for $C_{13}H_{19}O_4N$: OMe, 24·5%).

Lactone Formation.—Lactonisation of the syrup (0·3 g.) and distillation gave a syrupy product (0·21 g.) which showed $[\alpha]_D^{17}$ +30·8° (7 minutes); +38·4° (20 hours); +44·2° (48 hours); +45·2° (96 hours, constant) (*c*, 1·04 in water). A portion of the lactone was twice redistilled, but no significant difference in rotation figures was observed (Found: OMe, 33·6. Calc. for $C_7H_{12}O_5$: OMe, 35·3%). The lactone (20·8 mg.) required 4·80 c.c. of 0·0249N-sodium hydroxide for neutralisation (calc. for $C_7H_{12}O_5$: 4·75 c.c.). The lactone (41·0 mg.) was heated with sodium hydroxide (1N.; 0·5 c.c.) at 50° for 15 minutes. Water (1·5 c.c.) was added and the solution treated with periodic acid (Reeves, *loc. cit.*). This treatment gave the formaldehyde–dimedon compound (26·0 mg.), m. p. and mixed m. p. 188°. Treatment of the lactone with methanolic ammonia gave a syrupy amide, $[\alpha]_D^{17}$ +43° (*c*, 0·63 in water), which showed a negative Weerman test.

Methylation.—Fraction (4) (85 mg.) was treated with methanolic hydrogen chloride (3%; 20 c.c.) at 80° for 15 hours, to give a non-reducing syrup which was methylated 3 times with silver oxide and methyl iodide. The product on distillation at 80—100°/0·01 mm. was a highly mobile syrup (29 mg.) (Found: OMe, 58·4%). Hydrolysis was effected with nitric acid (2%; 7 c.c.) at 100°. $[\alpha]_D^{18}$ was +41° (zero time); +31° (1 hour); +15° (3 hours, constant). Appropriate treatment gave a syrup (17 mg.) identified on the paper chromatogram as trimethyl xylopyranose.

Fraction (5).—This crystallised completely. Trituration with acetone–light petroleum (1 : 3) gave 2 : 4-dimethyl β-D-xylose, m. p. 111°, not depressed on admixture with an authentic specimen. $[\alpha]_D^{19}$ was −13° (7 minutes); −1·5° (17 minutes); +9° (31 minutes); +19° (64 minutes); +21·5° (3 hours); +23° (24 hours, constant) (*c*, 2·1 in water) (Found: C, 47·3; H, 7·75; OMe, 34·7. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9; OMe, 34·8%). Lactonisation of this material gave syrupy 2 : 4-dimethyl xylonolactone, $[\alpha]_D^{17}$ −12° (15 minutes); −9° (2¼ hours); +15° (22 hours); +26° (46 hours); +27° (120 hours, constant) (*c*, 1·90 in water) (Barker, Hirst, and Jones, *loc. cit.*). Treatment with methanolic ammonia gave the syrupy amide, which showed a negative Weerman test, and on oxidation with periodic acid gave no formaldehyde.

Examination of Fraction (6).—Paper chromatography indicated the presence of 3-methyl xylose only, by direct comparison with a control. $[\alpha]_D^{19}$ +23° (*c*, 1·52 in water) was recorded.

Examination of Fraction III.—Fraction III (6·56 g.) was hydrolysed with nitric acid (2%; 150 c.c.) at 100°. $[\alpha]_D^{18}$ was +39° (1 hour); +24° (3 hours); +19° (6 hours, constant). This yielded a reducing syrup (4·92 g.) (Found: OMe, 18·2%). A fractionation was effected by means of a column of cellulose (27″ × 1·2″) with butanol (60%)–light petroleum (40%) saturated with water as eluent, to give four main fractions: (*a*) 0·95 g., (*b*) 2·26 g., (*c*) 0·44 g., and (*d*) 0·60 g. Recovery was 4·25 g. (92%).

Fraction (*a*), on examination by the paper chromatogram, was shown to consist mainly of 2 : 4-dimethyl xylose, with some 2 : 3-dimethyl xylose and a trace of the 2 : 6-dimethyl hexose component, while fractions (*b*), (*c*), and (*d*) showed the presence of monomethyl xyloses and/or arabinoses only.

Fraction (*a*) (0·80 g.) was oxidised, and distillation at 140—160°/0·05 mm. gave a syrupy lactone (0·53 g.) (Found: OMe, 33·4. Calc. for $C_7H_{12}O_5$: OMe, 34·8%), $[\alpha]_D^{18}$ +12° (5 minutes); +13·5° (1 hour); +15° (5 hours); +24° (24 hours); +27° (50 hours, constant) (*c*, 1·265 in water). The lactone (12·65 mg.) required 2·98 c.c. of 0·0249N-sodium hydroxide for neutralisation (Calc. for $C_7H_{12}O_5$: 2·89 c.c.). Treatment with methanolic ammonia yielded a syrupy amide which gave a negative Weerman test. Oxidation (of 41 mg.) with periodic acid gave formaldehyde as the dimedon compound (13 mg.), m. p. and mixed m. p. 187°.

Fraction (*b*) partly crystallised when kept. The crystalline material (1·50 g.) was separated by drainage on a tile and showed $[\alpha]_D^{17}$ +45° (5 minutes); +32° (17 minutes); +23° (50 minutes); +19° (19 minutes, constant) (*c*, 1·58 in water). Recrystallisation (absolute ethanol) gave 3-methyl D-xylopyranose as hygroscopic white needles, m. p. 95°, not depressed on admixture with an authentic specimen (Found: C, 42·7; H, 7·4; OMe, 21·0. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·4; OMe, 18·9%). Exhaustive extraction, with boiling acetone, of the tile used in separating the crystalline component gave a syrup (0·40 g.), $[\alpha]_D^{17}$ +25° (*c*, 4·0 in water), which was oxidised to the lactone. Distillation at 160—170°/0·025 mm. gave 3-methyl γ-D-xylonolactone (0·20 g.) as a syrup which rapidly crystallised. On recrystallisation (ethyl acetate–light petroleum), this had m. p. 90°, not depressed on admixture with an authentic specimen; $[\alpha]_D^{17}$ +72° (zero time); +45° (245 hours); +40° (600 hours, constant) (*c*, 0·88 in water) (Found: OMe, 18·0. Calc. for $C_6H_{10}O_5$: OMe, 19·1%).

Fraction (*c*) (0·22 g.), on treatment with alcoholic aniline, gave crystalline 3-methyl D-xylose anilide as the sole product, which on recrystallisation from ethyl acetate had m. p. and mixed m. p. 137° (Found:

C, 59·9; H, 7·1; N, 5·85; OMe, 12·5. Calc. for $C_{12}H_{17}O_4N$: C, 60·2; H, 7·2; N, 5·9; OMe, 12·9%).

Fraction (*d*) (0·40 g.) was oxidised to the lactone. The product was crystalline 3-methyl γ-D-xylonolactone, m. p. and mixed m. p. 94°, $[\alpha]_D^{17}$ +73° (5 minutes); +67° (6 hours); +63° (27 hours); +54° (120 hours); +48° (246 hours); +39° (510 hours, constant) (*c*, 0·685 in water). The lactone (8·22 mg.) required 2·20 c.c. of 0·0249N-sodium hydroxide for neutralisation (Calc. for $C_6H_{10}O_5$: 2·04 c.c.) (Found: C, 44·0; H, 6·47; OMe, 17·5. Calc. for $C_6H_{10}O_5$: C, 44·4; H, 6·2; OMe, 19·1%).

Examination of Fraction IV.—Fraction IV (0·88 g.) was hydrolysed with nitric acid (2%; 50 c.c.) at 100°. $[\alpha]_D^{18}$ was +41·5° (zero time); +32° (1 hour); +18° (3 hours); +15° (5 hours, constant). The solution was neutralised with barium carbonate, filtered, evaporated to dryness, and exhaustively extracted with boiling absolute methanol. The extracts were combined, evaporated to small volume, refiltered, and evaporated to dryness, to give a reducing syrup (0·70 g.) (Found: OMe, nil). Examination by means of the paper chromatogram gave xylose only, and the presence of D-xylose was confirmed by the isolation of the crystalline dimethyl acetal, m. p. and mixed m. p. 206°, of dibenzylidene D-xylose.

Examination of Fraction V.—Fraction V (3·93 g.) was hydrolysed with nitric acid as before. $[\alpha]_D^{17}$ was +18° (70 minutes); +7° (3 hours); +5° (6 hours, constant). This gave a reducing syrup (3·00 g.) which partly crystallised to give trimethyl α-D-xylopyranose (1·50 g.), m. p. and mixed m. p. 89°. The residual syrup (1·08 g.) on the paper chromatogram indicated trimethyl xylose and/or trimethyl arabinose along with small amounts of components of fraction VI.

Examination of Fraction VI.—Fraction VI (0·20 g.) was hydrolysed with nitric acid. $[\alpha]_D^{17}$ was +24° (1 hour); +18·5° (3 hours); +16° (5 hours, constant). This gave a reducing syrup (0·15 g.), which on the paper chromatogram indicated presence of trimethyl xylose and/or trimethyl arabinose (trace), tetramethyl galactose (trace), 2 : 6-dimethyl hexose, 2 : 3-dimethyl xylose, 2 : 4-dimethyl xylose, and 3-methyl xylose (trace).

Examination of Fraction VII.—Fraction VII (0·74 g.) was hydrolysed with nitric acid. $[\alpha]_D^{17}$ was +24° (1 hour); +17° (2 hours); +14° (4 hours); +13° (6 hours, constant). The syrup (0·54 g.) obtained, on investigation by means of the paper chromatogram, was found to contain the same components as fraction II.

Examination of Fractions VIII and IX.—These syrups were combined and the product (4·01 g.) hydrolysed with nitric acid. $[\alpha]_D^{18}$ was +34° (1 hour); +22° (3 hours); +18° (6 hours, constant). Appropriate treatment gave a syrup (3·00 g.) which, on investigation by the paper chromatogram, disclosed xylose, 3-methyl xylose, and smaller amounts of 2 : 4-dimethyl xylose, 2 : 3-dimethyl xylose, and 2 : 6-dimethyl hexose.

Formic Acid from PII.—The polysaccharide was oxidised with potassium periodate (Halsall, Hirst, and Jones, *J.*, 1947, 1427), and the formic acid liberated was determined by titration with 0·01N-sodium hydroxide with the following results, expressed in mols. of formic acid/g.: 0·00129 (1 day); 0·00182 (3 days); 0·00217 (6 days); 0·00234 (10 days, constant).

Periodate Uptake of PII.—Product PII (*ca.* 0·4 g.) was dissolved in water (50 c.c.), and sodium metaperiodate (0·4M.; 25 c.c.) added. Portions (5 c.c.) were withdrawn at intervals, and the periodate content was determined by the arsenite method, with the following results, expressed in mols. of periodate consumed per g.: 0·00312 (10 minutes); 0·00535 (15 minutes); 0·00638 (1 day); 0·00674 (3 days, constant).

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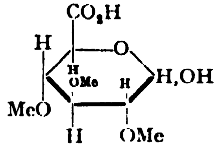
102. *The Structure of Peach Gum. Part I. The Sugars produced on Hydrolysis of the Gum.*

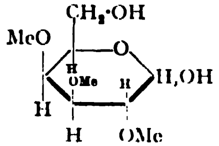
By J. K. N. Jones.

Peach gum on hydrolysis yields a mixture of D-galactose (5 parts), L-arabinose (6 parts), D-xylose (2 parts), rhamnose (*ca.* 2%), and D-glucuronic acid (1 part). The rate of hydrolysis indicates that the arabinose residues are in the furanose form; the other sugars are probably present in the pyranose form. Graded hydrolysis of the gum gives an aldobiuronic acid identified as 6-D-glucuronosido-D-galactose. Oxidation of the gum with periodic acid yields approximately two mols. of formic acid per repeating unit of equivalent weight 2040. Eight sugar residues are oxidised, of which four are arabinose, two are xylose and two are galactose.

SAMPLES of peach gum (*Prunus persica* L.) were kindly supplied from Piedmont, Italy, by Professor A. Nasini of the University of Turin, and from Bristol by Mr. R. Stitch. Examination of the physical constants of fractions of the gum indicated that it was essentially homogeneous, but it may be a mixture not separable by the methods in general use. Analysis of the sugars produced on hydrolysis of the fractions, by the use of partition chromatography (Flood, Hirst, and Jones, *J.*, 1948, 1679; Hirst and Jones, *J.*, 1949, 1659), showed that the ratio of sugars was D-galactose (5 parts), L-arabinose (6 parts), D-xylose (2 parts), and D-glucuronic acid (1 part; by difference) per equivalent weight of 2040. L-Rhamnose (*ca.* 2%) was also present. The identity of the sugars was confirmed by graded hydrolysis of the gum. The rate of hydrolysis of the sugars, estimated by chromatographic analysis on paper, showed that L-arabinose was hydrolysed very rapidly, indicating that it is combined in the furanose form in the gum (cf. damson gum; Hirst and Jones, *J.*, 1946, 506). The D-xylose was hydrolysed rather more slowly than the arabinose, but faster than the D-galactose, which is very probably in the pyranose form. From the products of hydrolysis of the gum, pure crystalline specimens of L-arabinose, D-galactose, D-xylose, and L-rhamnose were isolated. Oxidation of the gum with potassium periodate solution led to the consumption of ten moles of periodate and the formation of approximately two moles of formic acid per equivalent of gum (2040). During this oxidation all the xylose and approximately two-thirds (4 moles) of the arabinose and two-fifths (2 moles) of the galactose are destroyed. These results follow from a quantitative analysis of the sugars present in the oxidised gum by paper partition chromatography. Some of the L-arabofuranose residues must therefore be linked through $C_{(2)}$ and/or $C_{(3)}$ because only thus will the α-glycol group [·CH(OH)·CH(OH)·] be absent in the molecule. The formic acid may have arisen from the oxidation of a D-xylopyranose, a D-galactopyranose, or a uronic acid end group. If the D-xylose was an end group, then galactopyranose residues containing 1 : 2- or 1 : 4-glycosidic linkages were present in the gum. If the galactose residues occupy terminal positions, then xylose residues substituted on $C_{(2)}$ or $C_{(4)}$ only must be present in the gum molecule.

(I.)





(II.)

Methylation of the barium salt of the aldobiuronic acid fraction, obtained by graded hydrolysis of the polysaccharide, yielded a non-reducing methylated aldobiuronic acid which was built up of D-glucuronic acid linked through $C_{(6)}$ of a D-galactose residue, since on hydrolysis the methylated acid gave equimolecular proportions of 2 : 3 : 4-trimethyl D-glucuronic acid (I) and 2 : 3 : 4-trimethyl D-galactose (II). The former was identified as the crystalline methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, and the identity of (II) was confirmed from its rate of movement on the paper chromatogram and by the formation of its characteristic anilide. The aldobiuronic acid is therefore composed of the same sugar residues as are the aldobiuronic acids present in arabic acid and egg plum gum.

EXPERIMENTAL.

The crude samples of gum consisted of a mixture of large and small nodules admixed with bark and organic debris. The gum was essentially homogeneous since nodules gave, after purification, substantially identical constants. The gum was fractionated by extracting separate nodules successively with (*a*) cold water, yielding a cold-water fraction, and (*b*) hot N-sodium hydroxide to give an alkali-soluble fraction. The insoluble residue consisted of bark and inorganic material. The fractions were purified by precipitation from aqueous solution with glacial acetic acid (twice) (Bell and Young, *Biochem. J.*, 1934, **28**, 882). This procedure removed practically all the ash and colouring matter. The gum was finally precipitated from aqueous solution by addition of methanol in order to remove acetic acid. It was thus obtained as a white powder, initially freely soluble in water, but gradually becoming insoluble. Drying in a partial vacuum rapidly caused the gum to become insoluble in water. The cold-water-soluble fraction had $[\alpha]_D^{20}$ −46° (*c*, 0·23 as the sodium salt in water) (Found : equiv., 2500; sulphated ash, 0·4%). The gum soluble in hot sodium hydroxide had $[\alpha]_D^{20}$ −47° (*c*, 0·22 as the sodium salt in water) (Found: equiv., 2200; sulphated ash, 0·3%). Samples of gum from Turin and from Bristol were not distinguishable by physical properties or chemical reactions.

A sample of each of these fractions was hydrolysed on the boiling water-bath with N-sulphuric acid for 5 hours. The cooled solution was neutralised with barium carbonate and filtered, and the filtrate examined on the paper chromatogram; galactose, arabinose, and xylose were detected in each case. Rhamnose was not detected until a later stage (see below).

Quantitative Analysis of the Sugars produced on Hydrolysis of the Gum.—Peach gum (cold-water-soluble; 100·4 mg.) was hydrolysed with N-sulphuric acid (5 c.c.) in a sealed tube in a boiling water-bath for 12 hours. The cooled tube was opened and its contents were added to a solution of ribose (41·6 mg.); acids (including uronic acids) were then removed with Amberlite Resin IR4B, and the filtered solution was concentrated to about 2 c.c. Portions (0·001 ml.) of the solution were then placed on the starting line of a sheet paper chromatogram, an Agla micrometer syringe being used, and the sugars were separated and isolated by the procedure of Flood, Hirst, and Jones (*J.*, 1948, 1679) as modified by Hirst and Jones (*J.*, 1949, 1659) (Found: galactose, 0·93; arabinose, 0·93; xylose, 0·34; ribose, 0·90 mg.; whence the percentage of galactose is 38·6 calc. as $C_6H_{10}O_5$, and that of arabinose 37·8 and of xylose 13·8 calc. as $C_5H_8O_4$). A polysaccharide of equiv. 2040 and containing five galactose residues, six arabinose residues, two xylose residues, and one uronic acid residue per average repeating unit requires: galactose, 39·6 (calc. as $C_6H_{10}O_5$); arabinose, 38·8; xylose, 12·9% (calc. as $C_5H_8O_4$). Peach gum (soluble in sodium hydroxide) on hydrolysis and analysis, by the method detailed above, gave a mixture of galactose, arabinose, and xylose [Found: galactose, 40·2 (calc. as $C_6H_{10}O_5$); arabinose, 38·4; xylose 13·6% (calc. as $C_5H_8O_4$)]. Owing to the small amount present, rhamnose was not detected in these analyses.

Oxidation of Peach Gum with Potassium Periodate Solution.—The gum (547 mg. of neutral sodium salt) was dissolved in water (50 c.c.) containing potassium chloride (5 g.), sodium metaperiodate solution (50 c.c.; 0·25M.) added, and the whole shaken in the dark and in an air-tight vessel. After various time intervals, portions (25 c.c.) of the solution were withdrawn, ethylene glycol (excess) was added, and the formic acid titrated with 0·01N-sodium hydroxide, methyl-red being used as indicator [Found: 12·7 c.c. (190 hours); 12·5 c.c. (220 and 260 hours)]. This corresponds to the production of one mol. of formic acid per 1100 g. of gum, or approx. two mols. per equivalent of 2040.

The gum (516 mg.), under conditions of oxidation similar to those described above, consumed sodium periodate (4·9 c.c.; N.), whence 1 l. of M-periodate is equivalent to 211 g. of gum. It follows that approx. ten mols. of periodate are consumed per 2040 g. of gum.

Determination of the Sugars produced on Hydrolysis of the Oxidised Gum.—The gum (0·50 g.) was oxidised with potassium periodate as described above. Ethylene glycol was added to the solution after 200 hours, and the solution dialysed against distilled water until iodate and chloride ions could no longer be detected in the solution. The oxidised product (0·3 g.) was isolated by concentrating the dialysed solution to *ca.* 10 c.c. and precipitating it with methanol. The product, a pale yellow powder, was dried in a partial vacuum at 100°.

The oxidised polysaccharide (104·9 mg.) was hydrolysed by heating it with sulphuric acid (2N.; 5 c.c.) in a sealed tube in a boiling water-bath for 7 hours. The tube was cooled and the contents washed into a solution of ribose (89·3 mg.) in water. The solution was neutralised with Amberlite Resin IR4B and filtered. The filtrate was concentrated to *ca.* 1 c.c., and portions of the solution (0·001 ml.) were placed on the starting line of a sheet paper chromatogram. After separation and isolation the sugars were determined as before [Found: galactose, (*a*) 1·51, (*b*) 1·50; arabinose, (*a*) 0·57, (*b*) 0·61; ribose, (*a*) 4·35, (*b*) 4·45 mg.]. These figures correspond to the presence of the following percentage of sugars, calculated as $C_6H_{10}O_5$ and $C_5H_8O_4$, respectively: galactose, (*a*) 26·6, (*b*) 25·8; arabinose, (*a*) 10·0, (*b*) 10·4. No xylose could be detected.

Hydrolysis of Ash-free Peach Gum.—The gum (1·0 g.) was dissolved in 0·5N-sulphuric acid (25 c.c.) containing ribose (0·198 g.). The solution was heated in a closed vessel on a boiling water-bath, and at intervals samples were withdrawn and analysed [Found (reducing sugar calculated as hexose): 874 mg. (1 hour); 969 mg. (2 hours); 1·269 mg. (5 hours and 9 hours)].

Portions of the solution were withdrawn at intervals, cooled, neutralised with barium carbonate, and filtered, and the filtrate concentrated. The residual solution of sugars were analysed by the method of sheet paper chromatography [Found (percentage of sugars calc. as $C_6H_{10}O_5$ and $C_5H_8O_4$, respectively): galactose, 6·8; arabinose, 35; xylose, 8 (1 hour); galactose, 27·0; arabinose, 37·0; xylose, 13·3 (4 hours); galactose, 38·8; arabinose, 37·0; xylose, 12·8 (9 hours)]. Rhamnose was not detected in this experiment.

Autohydrolysis of the Gum.—The ash-free gum (10·52 g.) was dissolved in water (100 c.c.), and the thick brown solution heated on the steam-bath for 66 hours. At intervals, samples were withdrawn and analysed. It was not possible to follow changes in optical rotation owing to the darkness of the solution. Analysis on the paper chromatogram showed that arabinose was the first reducing sugar to appear in solution and that, after 41 hours, arabinose, xylose, and three other sugars, possibly disaccharides (their rate of movement on the paper chromatogram was about that of maltose), were present in the solution. After 52 hours, galactose, arabinose, and xylose could be detected. At this stage, the solution contained 5·4 g. of reducing sugars (calc. as hexose). This figure remained unaltered on heating of the solution for a further 14 hours.

The cooled solution was neutralised with barium hydroxide solution and filtered. The filtrate was concentrated to *ca.* 100 c.c. and poured into methanol (1 l.). The precipitated barium salts were redissolved in water and reprecipitated in methanol to remove reducing sugars, yielding a product (*A*, 2·75 g.) containing no free galactose, arabinose, or xylose (paper chromatogram). The methanolic solution on concentration gave a syrup which was exhaustively extracted with boiling methanol, yielding an alcohol-insoluble residue (*B*; 1·7 g.) and soluble sugars (*C*; 7·5 g.) obtained on removal of the solvent.

Fraction (*C*) crystallised on trituration with methanol. The crystals (3·66 g.) were filtered off and identified as L-arabinose, $[\alpha]_D^{20}$ 105° (in water), m. p. 160°. These crystals contained traces of xylose only as impurity (paper chromatogram). The non-crystalline residue was analysed on the paper chromatogram [Found: galactose, 1·27; arabinose, 0·75; xylose, 0·66 mg.; whence the weights of galactose, arabinose, and xylose present in the syrup (3·84 g.) were 1·81, 1·07, and 0·95 g., respectively]. The presence of these sugars was confirmed by the isolation of L-arabinose benzoylhydrazone, m. p. 186°, D-galactose phenylmethylhydrazone, m. p. and mixed m. p. 186°, and dibenzylidene D-xylose dimethyl acetal, m. p. 210°, not depressed on admixture with an authentic specimen. L-Rhamnose was not detected until later (see below).

The syrupy sugars (3·0 g.) from fraction (*C*) were separated on a column of cellulose by the method of Hough, Jones, and Wadman (*J.*, 1949, 2511), using *n*-butanol saturated with water as eluent. Examination of the eluate showed that the first tubes contained pure L-rhamnose, which was isolated as the crystalline hydrate (52 mg.) after recrystallisation from acetone–methanol, m. p. and mixed m. p. 100°, $[\alpha]_D$ +9° (*c*, 1·1 in water). The next few tubes contained D-xylose, which was obtained crystalline on concentration of the solvent. After recrystallisation, the product had m. p. 146° and $[\alpha]_D$ +18° (in water). Thereafter arabinose and galactose were eluted from the column but were not further examined. The residual sugars on the column were then eluted with water, the eluate was concentrated, and the residual syrupy sugars (0·52 g.) separated by the filter-paper strip method of Flood, Hirst, and Jones (*loc. cit.*), yielding the following fractions: (*a*) arabinose, (*b*) galactose, (*c*), (*d*), and (*e*) sugars moving at a rate corresponding closely to that of a disaccharide. Fractions (*a*) and (*b*) were not further examined. Fraction (*e*), which had moved very slowly indeed, was a barium salt and was discarded. Fractions (*c*) and (*d*) on hydrolysis yielded galactose, identified by its rate of movement on the chromatogram.

Fraction (*B*) (1·7 g.) was hydrolysed with 0·5N-sulphuric acid (50 c.c.) on the boiling water-bath: $[\alpha]_D^{20}$ rose to +47° (*c*, 3·4 in 0·5N-sulphuric acid; constant value, 6 hours). The cooled solution was neutralised with barium carbonate and filtered. The filtrate was concentrated, and the syrupy residue extracted exhaustively with methanol, leaving an insoluble barium salt (0·8 g.). The methanol extract contained galactose (0·82 g.), arabinose (0·07 g.), and xylose (0·04 g.), determined by analysis on the paper chromatogram. D-Galactose was further identified by the isolation of the crystalline sugar (0·6 g.), m. p. 165°, $[\alpha]_D^{20}$ +82° (in water). The insoluble residue of barium salt (0·8 g.) was added to the barium salt obtained from fraction (*A*) (see below).

Fraction (*A*) (2·03 g.) was hydrolysed with boiling 0·1N-sulphuric acid (75 c.c.) for 12 hours: $[\alpha]_D$ rose from +29° to +47°. The cooled solution was neutralised with barium hydroxide solution and filtered, the filtrate concentrated to dryness, and the residue exhaustively extracted with methanol, leaving a barium salt (1·58 g.). Concentration of the methanolic extract gave crystalline D-galactose (0·46 g.), $[\alpha]_D^{20}$ +80°, m. p. 165°. This sample of sugar contained traces of arabinose and xylose (paper chromatogram).

Identification of Uronic Acid Fraction.—The barium salts (1 g.) from fraction (*A*) (above) were heated with sulphuric acid (2N.; 25 c.c.) for 15 hours on the boiling water-bath to hydrolyse any remaining oligosaccharide. The cooled solution was then neutralised (a small quantity of the syrup was examined on the paper chromatogram and spots corresponding to the presence of glucurone and glucuronic acid were detected), and the sugars were converted into their methyl ethers by reaction first with methyl sulphate and sodium hydroxide until the solution was non-reducing to Fehling's reagents, and then by the addition of 30% sodium hydroxide and methyl sulphate with stirring. After completion of the addition of the reagents, the solution was boiled to destroy sodium methyl sulphate, cooled, extracted with chloroform, acidified, and again extracted with chloroform. Concentration of the latter chloroform extracts yielded trimethyl methyl-D-glucuronoside (0·42 g.) as a syrup (Found: OMe, 49·0%; equiv., 254. Calc. for $C_{10}H_{18}O_7$: OMe, 49·6%; equiv., 250). The D-glucuronoside (0·4 g.) was hydrolysed with N-hydrochloric acid on the boiling water-bath for 5 hours, the solution cooled, and bromine water added. When the solution no longer reduced Fehling's solution (5 days) it was aerated to remove bromine, neutralised with silver carbonate, filtered before and after the passage of hydrogen sulphide, and then concentrated to the syrupy 2 : 3 : 4-trimethyl D-glucosaccharic acid. This product was esterified by boiling it with methanolic hydrogen chloride, and the solution was then neutralised with silver carbonate and filtered. Concentration of the filtrate yielded the methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, m. p. and mixed m. p. 111°.

Isolation of a crystalline acid derivative. The residual barium salts (1·15 g.) from fractions (*A*) and (*B*) were methylated with methyl sulphate and sodium hydroxide by the procedure described above. After completion of the methylation, the solution was cooled, acidified with dilute sulphuric acid, and extracted with chloroform. Concentration of the extracts left a syrup (0·8 g.) which was methylated with Purdie's reagents and then distilled. Two fractions and a still residue were obtained: Fraction (1) (0·11 g.), b. p. 130°/0·05 mm., n_D^{18} 1·4484 (Found: OMe, 50·0%); this fraction on hydrolysis gave 2 : 3 : 4-trimethyl D-glucuronic acid, identified by its rate of movement on the chromatogram and by its conversion into the methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, m. p. 111°. Fraction (2) (0·23 g.), b. p. 200—230°/0·05 mm., n_D^{20} 1·4662 (Found: OMe, 51%; equiv., 450). Still residue (0·42 g.) (Found: OMe, 40·3%). Fraction (2) (0·20 g.) was hydrolysed with 2N-hydrochloric acid (25 c.c.) for 15 hours. It was not possible to follow any change in optical rotation owing to darkening of the solution. The solution was neutralised with silver carbonate and filtered, and the filtrate treated with hydrogen sulphide and again filtered. The filtrate was concentrated to 10 c.c. and then neutralised with barium carbonate and filtered. Concentration of the filtrate left a glass which was exhaustively extracted with ether, leaving the barium salt of 2 : 3 : 4-trimethyl D-glucuronic acid, identified as the methyl ester of 2 : 3 : 4-trimethyl D-glucosaccharolactone, m. p. and mixed m. p. 111°. The ethereal extract contained 2 : 3 : 4-trimethyl D-galactose, since a small quantity of the syrup remaining after removal of the solvent moved at the same rate as this compound on the paper chromatogram (Brown, Hirst, Hough, Jones, and Wadman, *Nature*, 1948, **161**, 720). This was confirmed by converting the syrup {0·08 g.; $[\alpha]_D^{21}$ +87° (*c*, 0·8 in water)} into the characteristic anilide, m. p. 169°, not depressed on admixture with an authentic sample.

THE UNIVERSITY, BRISTOL.

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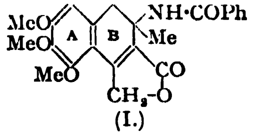
103. *Colchicine and Related Compounds. Part X.*

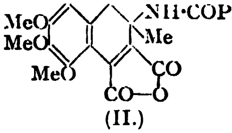
By J. W. COOK, T. Y. JOHNSTON, and J. D. LOUDON.

6 : 7 : 8-*Trimethoxy*-3-*methylnaphthalene*-1 : 2-*dicarboxylic acid anhydride* (VII) has been obtained by dehydrogenation of the 3 : 4-*dihydronaphthalene* derivative (VI) which, in turn, has been synthesised from *iso*elemicine and chloromaleic anhydride. *N*-Benzoylcolchinic anhydride, formulated by Windaus as (II), does not behave as a dihydronaphthalene derivative since it has now been deaminated to *deaminocolchinic anhydride* which (*a*) is isomeric, and not identical, with 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride (VII), and (*b*) has olefinic properties as shown by its susceptibility to hydrogenation with a palladium catalyst. Deaminocolchide also has olefinic properties. Oxidation of colchiceine and of *N*-acetylcolchinol to the same product, namely, N-*acetylcolchinic anhydride*, indicates that the size of ring B is the same in the colchinic acid as in the colchinol series of colchicine degradation products.

ACCORDING to Windaus (*Annalen*, 1924, **439**, 59) hydronaphthalene derivatives are produced when *N*-benzoyltrimethylcolchicinic acid is oxidised with cold alkaline potassium permanganate. The two main products, namely, *N*-benzoylcolchide and *N*-benzoylcolchinic anhydride, were formulated as (I) and (II), respectively, although minor modification, particularly in the structure (I), was not excluded. This interpretation accounted for the known facts and contributed to the conclusion that ring B of colchicine is six-membered. It has since been established, however, that in another series of degradation products ring B occurs as a seven-membered ring (Barton, Cook, and Loudon, Part V, *J.*, 1945, 176; Buchanan, Cook, Loudon, and MacMillan, *Nature*, 1948, **162**, 692), and in consequence re-examination of the supposed hydronaphthalene structures becomes desirable. It is consistent with the dihydronaphthalene structure (I) that *N*-benzoylcolchide eliminates benzamide during hydrolysis or sublimation (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat. Kl., *A*, 1911, 2 Abh.). The deaminocolchide so produced was regarded as the "trimethoxyhomonaphthide" (III), and it might be expected on this basis that the corresponding acid anhydride (VII) would be formed either by oxidation of deaminocolchide or by deamination of *N*-benzoylcolchinic anhydride. Accordingly, the *compound* of structure (VII) has been synthesised for reference purposes.



(I.)



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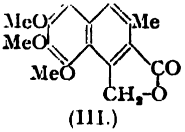
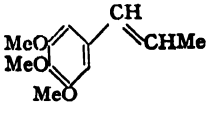


(III.)

Hudson and Robinson (*J.*, 1941, 715) recorded successful condensations of the Diels–Alder type between β-alkylated styrenes and either maleic anhydride or ethyl acetylenedicarboxylate. More recently Synerholm (*J. Amer. Chem. Soc.*, 1945, **67**, 345) reported good results by use of chloromaleic anhydride, which is satisfactorily prepared from chlorofumaric acid (Perkin, *J.*, 1888, **53**, 695) by Walden's method (*Ber.*, 1897, **30**, 2885; cf. von Auwers and Harres, *ibid.*, 1929, **62**, 1686). The diene component for our synthetic work, namely, 3 : 4 : 5-trimethoxypropenylbenzene (IV), is already known as *iso*elemicine and was prepared by Semmler (*Ber.*, 1908, **41**, 2186), who obtained it through isomerisation of elemicine, the naturally occurring 3 : 4 : 5-trimethoxyallylbenzene. Although elemicine may be prepared from the allyl ether of 2 : 6-dimethoxyphenol (Hahn and Wassmuth, *Ber.*, 1934, **67**, 696; Pearl, *J. Amer. Chem. Soc.*, 1948, **70**, 1746) and might therefore be used as a source of *iso*elemicine, we have prepared the latter by dehydrating the carbinol which is produced from 3 : 4 : 5-trimethoxybenzaldehyde and ethylmagnesium bromide.

A preliminary experiment showed that, under the conditions used by Hudson and Robinson, condensation between *iso*elemicine and maleic anhydride was accompanied by much polymerisation although the formation of (V) was indicated by isolation of the corresponding dibasic *acid* from which the *anhydride* itself was obtained on sublimation. The condensation of *iso*elemicine with chloromaleic anhydride was then examined in various solvents, and the *anhydride* (VI) was ultimately obtained in 45—50% yield by heating the reactants in xylene with the addition of quinol to inhibit polymerisation (cf. Norton, *Chem. Reviews*, 1942, **31**, 319). It might be expected from the work of Bergmann (*J. Amer. Chem. Soc.*, 1942, **64**, 176; *J. Org. Chem.*, 1943, **8**, 183) that condensation to the dihydronaphthalene derivative (VI) when conducted in nitrobenzene would be followed by dehydrogenation to the naphthalene derivative (VII), but in practice under these conditions dehydrogenation was not observed. On the other hand, when (VI) was submitted to slow sublimation there occurred disproportionation of hydrogen with formation of (VII) and (V), the latter again being isolated as the dibasic acid;



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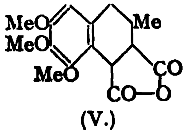

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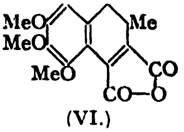
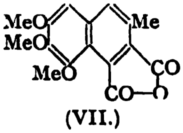


(VI.)



(VII.)

moreover, dehydrogenation of (VI) to (VII) was readily effected by heating with palladium in a current of carbon dioxide. In contrast to the tetrahydronaphthalene (V), which is colourless, the anhydrides (VI) and (VII) are yellow and orange respectively. All three anhydrides dissolved in alkali to give colourless solutions from which on acidification the colourless dibasic *acids* corresponding to (V) and (VI) were respectively obtained, but the acid corresponding to

(VII) rapidly reverted to the anhydride and was not analysed. The facility with which anhydrides are obtained from naphthalene-1 : 2-dicarboxylic acids has already been noted by Hudson and Robinson (*loc. cit.*) and our observations are consistent with increasing ease of formation in the order (V) $<$ (VI) $<$ (VII).

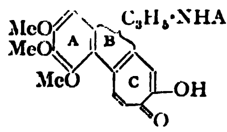
As expected, the naphthalene derivative (VII) was unaffected by exposure to hydrogenation conditions with a palladium catalyst, but under the same conditions an abnormal behaviour was shown by the dihydronaphthalene derivative (VI). This compound, dissolved in acetic acid, rapidly absorbed one mole of hydrogen and then, unexpectedly, slowly absorbed a second mole, the initial yellow colour of the solution being discharged only during the latter stage of absorption. Subsequent isolation of 6 : 7 : 8-trimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-dicarboxylic acid in considerable quantity showed that (V) is a major product of the reaction but the nature of the side reaction remains undetermined. The same dicarboxylic acid was formed by reduction of (VI) with zinc and acetic acid.

Part of the colchicine required for degradative work was purchased from Messrs. Ransom (Hitchin, Herts.) as the concentrates of an alcohol extract of *Colchicum* seeds, and the alkaloid was isolated by the procedure of Chemnitius (*J. pr. Chem.*, 1928, **118**, 29) combined with chromatographic purification (cf. Ashley and Harris, *J.*, 1944, 677). The derived *N*-benzoyltrimethylcolchicinic acid was prepared as described by Windaus (*loc. cit.*, 1911) but attempted repetition of his oxidation experiments on this compound gave much less satisfactory results. Although *N*-benzoylcolchide and *N*-benzoylcolchinic anhydride were both identified, the smallness of the yields severely restricted the scope of further degradative work. Moreover, even under the experimental conditions which are stated (Windaus, *loc. cit.*, 1911) to afford *N*-benzoylcolchide, the anhydride appeared to be the predominant product. In addition to benzamide, benzoic acid, and probably *N*-benzoylcolchinic acid, which were incidentally isolated, two unidentified oxidation products were obtained in small quantities and have not yet been examined in detail.

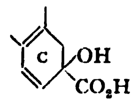
Thermal decomposition of *N*-benzoylcolchinic anhydride takes a different course from that described by Windaus for *N*-benzoylcolchide. The latter compound yields benzamide and deaminocolchide whereas it is now found that the anhydride yields benzamide only in traces; the main product of the decomposition is a neutral nitrogenous *substance* to which the provisional formula, $C_{21}H_{19}O_5N$, is assigned pending fuller investigation when an adequate supply of material becomes available. However, when heated with phosphoric oxide in xylene (cf. Cook and Graham, Part III, *J.*, 1944, 322; Cook, Dickson, Ellis, and Loudon, Part VII, *J.*, 1949, 1074), *N*-benzoylcolchinic anhydride yielded *deaminocolchinic anhydride*, and this compound proved to be quite distinct from the synthetic 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride (VII).

When subjected to quantitative micro-hydrogenation over a palladium catalyst neither *N*-benzoylcolchide nor *N*-benzoylcolchinic anhydride absorbed hydrogen, although the latter compound is already known (Windaus, *loc. cit.*, 1911) to contain one ethylenic linkage which can be reduced by means of zinc and acetic acid. It may be recalled that in both colchicine and colchiceine, apart from the aromatic ring, there is one double bond which resists catalytic hydrogenation (Bursian, *Ber.*, 1938, **71**, 245) and a similar resistant double bond therefore appears to be maintained in the above degradation products. On the other hand, both deaminocolchide—prepared as described by Windaus (*loc. cit.*, 1911) by hydrolysis of *N*-benzoylcolchide—and deaminocolchinic anhydride undergo hydrogenation with palladium as catalyst, absorbing one and two moles of hydrogen, respectively. The difference in the extent of hydrogenation is remarkable but, although it was ascertained that in each case a crystalline product results, shortage of material prevented further inquiry. None the less, the fact of hydrogenation under these conditions strongly indicates that the double bond which is produced in each case by deamination does not form part of an aromatic ring. In the same connection it may be noted that *N*-benzoylcolchide is not completely deaminated by six hours' heating with concentrated hydrochloric acid in ethanol. The amine, colchide, is a part-product of the reaction and consequently survives conditions which, if it were correctly formulated as (I; H for COPh), should readily transform it into the aromatic structure (III). These objections to a (hydro)naphthalene structure in the present compounds find their counterparts in objections which led to revision of the (hydro)phenanthrene structure in colchinol derivatives (Cohen, Cook, and Roe, Part I, *J.*, 1940, 194; Part V, *loc. cit.*). They suggest that the size of ring B may not in fact be different in the two sets of colchicine degradation products.

In the series of reactions by which colchiceine is converted into the dibenz*cyclo*heptatriene (XI) there appear to be only two opportunities for rearrangement in the carbon structure of ring B. These opportunities occur (i) dnring the change from colchiceine to *N*-acetylcolchinol (X; R = H), whereby ring C becomes aromatic, and (ii) in the deamination of *N*-acetylcolchinol methyl ether (X; R = Me) ⟶ (XI). The available evidence makes it rather unlikely that the size of ring B is affected at either stage. In particular, as discussed in Parts I, V, and VII, it is highly improbable that the deamination step involves expansion of a six- to a seven-membered ring. The process by which ring C becomes phenolic is more obscure, but in terms of Dewar's tropolone formula (VIII) for colchiceine (*Nature*, 1945, 155, 141) the change may proceed through (IX) and ultimately to (X; R = H) without involving ring B. This change, however, is still without analogy among other tropolone compounds, where aromatisation generally leads to a derivative of benzoic acid rather than of phenol. It is of considerable interest, therefore, that by means of alkaline potassium permanganate we have now been able to oxidise both colchiceine and *N*-acetylcolchinol to the same product, namely, *N*-acetylcolchinic anhydride which Windaus (*loc. cit.*, 1911) had already obtained from the first-named source, although he does not record analytical figures. The possibility of molecular rearrangement during the course of these oxidations cannot be excluded. Indeed, the preparation of *N*-acetylcolchinol from colchiceine involves oxidation—by hypoiodite, followed by reduction of the intermediate *N*-acetyliodocolchinol (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat.Kl., *A*, 1914, 18 Abh.), or by hydrogen, peroxide (Šantzavý, *Chem. Listy*, 1949, 43, 156)—in an alkaline medium and the course of oxidation with permanganate may well be similar. Even so, unless invalidated by the *renewed* incidence of rearrangement, the conclusion follows that the carbon structure of ring B is the same in colchinol as in colchinic anhydride.



(VIII.)



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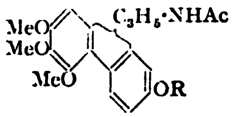
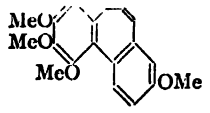


(X.)



(XI.)

In general, therefore, the results described serve to unify the problems relating to the structure of ring B in the two main series of the alkaloid's degradation products. Questions of detailed structure in individual compounds remain unsettled and to these we hope to devote our attention.

EXPERIMENTAL.

3 : 4 : 5-*Trimethoxyphenylethylcarbinol*.—A solution of 3 : 4 : 5-trimethoxybenzaldehyde (20·3 g.) in anhydrous ether (400 c.c.) was added with cooling and stirring to the Grignard reagent prepared from ethyl bromide (20 g.), magnesium turnings (4·5 g.), and ether (40 c.c.). After 16 hours at 0°, the mixture was treated with a saturated aqueous solution of ammonium chloride. The ethereal layer, combined with ethereal washings of the aqueous layer, was washed with water, concentrated, and shaken with aqueous sodium hydrogen sulphite which removed a little unchanged aldehyde. The carbinol, obtained by evaporating the solvent from the washed and dried ethereal solution, was a viscous, pale yellow liquid (23·15 g.).

iso*Elemicine*.—The carbinol, to which a crystal of iodine had been added, was heated under distillation conditions at diminished pressure and with a tower of sodium hydroxide pellets in the circuit to trap uncondensed vapours. Vigorous effervescence occurred at relatively low temperatures and *iso*elemicine (85—87%) was collected up to 150°/0·4 mm., was redistilled, showing b. p. 110—115°/0·4 mm. (Found : C, 68·9; H, 7·7. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·7%), and identified as the dibromide, m. p. 92—93° (Found : C, 39·5; H, 4·5. Calc. for $C_{12}H_{16}O_3Br_2$: C, 39·1; H, 4·35%) (Semmler, *loc. cit.*, gives m. p. 89—90°). Prepared in this way, the product was only slightly yellow and was accompanied by a small higher-boiling residue which afforded a second fraction, b. p. 204°/0·4 mm., as a yellow resin with violet fluorescence.

Less satisfactory yields of *iso*elemicine were obtained by heating the carbinol for 30 minutes at 160° with (*a*) dehydrated alum and some crystals of quinol (yield 46%) (cf. Barnett and Lawrence, *J.*, 1935, 1104) or (*b*) potassium hydrogen sulphate (yield 63%), whilst (*c*) with phosphoric oxide in boiling xylene or (*d*) with thionyl chloride in cold dry pyridine (cf. Ellis and Petrow, *J.*, 1939, 1081) the yields were very poor. In all of these cases the ether-soluble product, after distillation of *iso*elemicine, gave a high-boiling resin which in case (*b*) was heated for 1 hour at 140° with anhydrous oxalic acid and, after recovery in ether and washing with alkali, afforded a viscous fluorescent distillate, b. p. 200°/0·1 mm., which crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 187° (Found : C, 69·1; H, 7·6%), and was probably a dimer.

6 : 7 : 8-*Trimethoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-1 : 2-*dicarboxylic Acid and its Anhydride* (V).—A solution of *iso*elemicine (0·328 g.) and maleic anhydride (0·773 g.) in xylene (5 c.c.) was boiled under reflux for 8 hours and then left at room temperature for 2 days. Xylene and maleic anhydride were distilled off (up to 70°/0·6 mm.), and the residue, treated with ether, afforded an amorphous solid which was again heated (at 130°/0·1 mm.) to remove volatile material. Thereafter crystallisation from acetic acid gave the *acid* as colourless plates, initially melting at 197—198° but reverting on storage to m. p. 181—182° (Found : C, 59·2; H, 6·3. $C_{16}H_{20}O_7$ requires C, 59·3; H,

6·2%); when melted at atmospheric pressure and then sublimed at 200—210°/0·1 mm., the acid yielded the *anhydride*, micro-m. p. 93° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 63·0; H, 5·4. $C_{16}H_{18}O_6$ requires C, 62·75; H, 5·9%).

6 : 7 : 8-*Trimethoxy*-3-*methyl*-3 : 4-*dihydronaphthalene*-1 : 2-*dicarboxylic Acid and its Anhydride* (VI).—(*a*) A solution of *iso*elemicine (0·753 g.) and chloromaleic anhydride (2·4 g.) in dry nitrobenzene (8 c.c.) was heated under reflux for 1½ hours. Nitrobenzene and chloromaleic anhydride were distilled off (up to 61°/1 mm.) and the residue was treated with ether, an insoluble, dark product being discarded. Concentration of the solution gave the anhydride (0·29 g., 26%), m. p. 132—135° [from ether–light petroleum (b. p. 40—60°)].

(*b*) A mixture of *iso*elemicine (6·02 g.), chloromaleic anhydride (6 g.), xylene (18 c.c.), and a few crystals of quinol was heated under reflux for 23 hours. From the clear solution, filtered if necessary, there were distilled off (i) xylene under water-pump pressure and (ii) a mixture of chloromaleic anhydride and *iso*elemicine (up to b. p. 140°/0·3 mm.) from which the latter (0·218 g.) was recovered by treatment with alkali and redistillation. The non-volatile residue when treated with ether afforded yellow needles of the *anhydride* (4·346 g.), m. p. 134—135° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 63·1; H, 5·45. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%), and on concentration of the ethereal mother-liquor there first separated crystals of chlorofumaric acid (0·5 g.), m. p. and mixed m. p. 190—191°, and the remainder on extraction with alkali and acidification yielded an impure sample (0·126 g.) of the dibasic *acid* corresponding to (VI). The same acid was prepared by warming (VI) with 10% aqueous sodium hydroxide, followed by acidification of the cooled solution; it formed colourless crystals, m. p. 146—147° (effervescence) (from acetic acid), and appeared to retain solvent in the crystal (Found: C, 56·7; H, 5·6. $C_{16}H_{18}O_7,C_2H_4O_2$ requires C, 56·5; H, 5·8%), but gave the correct analytical figures—and same m. p. behaviour—after crystallisation from water (Found: C, 59·8; H, 5·5. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%).

When rapidly sublimed (½ hour) at 200°/0·1 mm., the acid yielded the anhydride (VI), m. p. and mixed m. p. 135°, but on slower sublimation at 190—200°/18 mm. the later fractions of the sublimate gave the dehydrogenated anhydride (VII), m. p. and mixed m. p. 190—192° (from acetic acid), whilst the mother-liquor on storage slowly deposited colourless plates of 6 : 7 : 8-trimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-dicarboxylic acid, m. p. and mixed m. p. 208° and 208—210°, respectively (effervescence). The same acid was obtained when a solution of the anhydride (VI) in acetic acid was heated for 3 hours at 100° with an excess of zinc dust, the product being recovered from the filtered solution and purified by passage in benzene through a column of silica gel.

6 : 7 : 8-*Trimethoxy*-3-*methylnaphthalene*-1 : 2-*dicarboxylic Anhydride* (VII).—The anhydride (VI) (0·71 g.), mixed with palladium (0·19 g.), was heated in a slow stream of dry carbon dioxide at 230—240° for 1½ hours. The product, which had partly sublimed, was recovered in ether and formed yellow needles, m. p. 194—194·5°, from ether (Found: C, 63·8; H, 4·65. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%). The anhydride was regenerated by dissolution in alkali and acidification.

Isolation of Colchicine.—A concentrated ethanolic extract of *Colchicum* seeds (333 g.; from Messrs. Ransom), diluted with water (450 c.c.), was heated with paraffin wax (75 g.), and the liquid mixture, after vigorous stirring, was cooled, the solidified wax layer was lifted off, and the aqueous layer was re-treated with fresh wax (75 g.). The wax layers were extracted with boiling water (3 × 100 c.c.), and the total aqueous solution was mixed with " Hyflo Supercel " (100 g.). After filtration, using a pre-coat of " Hyflo ", the filter-bed was well washed. The combined filtrates were exhausted with acid-free chloroform (12 × 200 c.c.) which, after being dried (K_2CO_3) and concentrated, afforded a brownish-yellow syrup. A solution of the syrup in chloroform (150 c.c.) was passed through a column of alumina (25 × 3·5 cm.; from B.D.H.; saturated with benzene) which retained much adsorbed material in several distinct zones (still under examination), and the colchicine was eluted by continued passage of chloroform until the eluate, initially yellow, became colourless and left no residue on evaporation. The recovered syrup was dissolved in ethanol which was then distilled off, the process being repeated thrice to ensure removal of chloroform. The final residue crystallised from ethyl acetate in fine colourless needles of m. p. 148—150° raised by renewed chromatography to m. p. 155°; $[\alpha]_D^{13}$ −119·9°, $[\alpha]_{5461}^{13}$ −167·8° (c = 0·878 in chloroform).

N-*Benzoylcolchinic Anhydride.*—A solution of *N*-benzoyltrimethylcolchicinic acid (3·24 g.) in 3% aqueous potassium hydroxide (32 c.c.) was treated (20 minutes) under cooling with 4% potassium permanganate (208 c.c.). After 12 hours the mixture was acidified with sulphuric acid and clarified by a stream of sulphur dioxide. A chloroform extract yielded an orange syrup which was dissolved in ethyl acetate, the solution was shaken with 2% aqueous sodium carbonate (which extracted acidic material including some benzoic acid), washed, and concentrated. When rubbed with benzene the residue afforded a brown solid (*A*) (0·477 g.), m. p. 193° (from benzene), and the benzene mother-liquor when passed through a short column of silica gel and eluted with benzene yielded (*a*) in the first colourless eluate, a few crystals of benzamide, m. p. and mixed m. p. 127°, and (*b*), in the yellow eluate, the anhydride, m. p. 201—202° (Windaus records m. p. 207°). Solid (*A*) when similarly purified afforded the anhydride as rectangular yellow plates, m. p. 201—202° (Found: C, 65·3; H, 4·8; N, 3·5. Calc. for $C_{23}H_{21}O_7N$: C, 65·25; H, 5·0; N, 3·3%). Recrystallisation from chloroform–ethyl acetate (1 : 1) gave the compound as flat rectangular plates, m. p. 211—212°.

In course of exploratory experiments on the purification of solid (*A*), combined benzene mother-liquors were passed through a column of alumina (B.D.H.) on which, however, adsorption was rather strong. Elution with benzene gave (i) a faintly yellow eluate which on concentration afforded stout, almost colourless crystals of a neutral *substance* (*B*), m. p. 164° (from benzene), recrystallising as colourless hexagonal plates, micro-m. p. 157° (from the same solvent) (Found: C, 69·7; H, 5·0; N, 4·2. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7; N, 3·9%. $C_{21}H_{19}O_5N$ requires C, 69·05; H, 5·2; N, 3·8%), and (ii) a yellow eluate, from which on concentration some benzamide crystallised, m. p. and mixed m. p. 127·5°.

Sublimation of N-*Benzoylcolchinic Anhydride.*—When the anhydride (0·09 g.) was heated at 220—230°/18 mm. in a sublimation apparatus the melt bubbled vigorously for about 30 minutes, and the slight yellow sublimate at this stage crystallised from benzene as a mixture of radiating yellow needles of unchanged anhydride (probably present as the result of splashing) and a few colourless rectangular plates of benzamide, micro-m. p. 122° raised to 124—126° by admixture with an authentic specimen. The subsequent orange-red sublimate, collected during 90 minutes while the temperature was gradually raised to 250—260°/18 mm. (leaving a non-volatile, uncrystallisable residue), afforded small colourless prisms, which had micro-m. p. 159—160° after several crystallisations from benzene (Found: C, 69·3; H, 5·25; N, 4·0; OMe, 25·0. $C_{21}H_{19}O_5N$ requires C, 69·05; H, 5·2; N, 3·85; OMe, 25·5%).

Evaporation of the first benzene mother-liquor from this *substance* afforded a semi-crystalline gum from which there was obtained a mixture of colourless prisms, micro-m. p. 170—171°, and yellow needles, micro-m. p. 196—206° (effervescence) (from aqueous acetic acid). These are probably secondary products and await further investigation.

Deaminocolchinic Anhydride.—A hot solution of *N*-benzoylcolchinic anhydride (90 mg.) in purified xylene (8 c.c.) was treated with phosphoric oxide (250 mg.), and the whole was heated under reflux for 20 minutes. The hot solution was decanted from the red gelatinous phosphoric residues which were then washed (*a*) with fresh boiling xylene (2 × 6 c.c.) and (*b*) with boiling chloroform (3 × 8 c.c.). The combined and cooled xylene solution was again decanted from a slight deposit of gelatinous substance and was then concentrated at 18 mm. The cooled concentrates deposited masses of golden-yellow rectangular plates or prisms of micro-m. p. 170—171° from benzene–light petroleum (b. p. 60—80°) (Found: C, 63·8; H, 4·7. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%). A further small quantity of the same *substance* was recovered from the chloroform washings (*b*). It was only slowly affected by cold, but dissolved in hot, dilute alkali giving a colourless solution.

Hydrogenation.—The product (5·36 mg.) in acetic acid (4 c.c.) and in presence of palladium black absorbed 0·90 c.c. of hydrogen at 20°/760 mm., corresponding to 2·1 double bonds. There was recovered from the still faintly yellow solution a gum which crystallised from benzene–light petroleum (b. p. 60—80°) as needles of micro-m. p. 108—110°.

N-*Benzoylcolchide.*—A solution of *N*-benzoyltrimethylcolchicinic acid (7 g.) in 2% potassium hydroxide (70 c.c.) was treated at 0—3° with 4% potassium permanganate (350 c.c.), and after 4 hours the manganese dioxide was filtered off and washed (i) with boiling water, the aqueous filtrates being combined, and (ii) with boiling ethanol, the (moist) solution on concentration affording a gummy solid in aqueous suspension. Separate extraction of the filtrate (i) and suspension (ii) with chloroform gave, after drying and recovery, brown amorphous solids (0·168 g. and 0·454 g., respectively), whilst, after concentration of the filtrate (i) to small bulk under reduced pressure and in a stream of carbon dioxide, renewed extraction afforded a further quantity (0·917 g.) of a similar solid. Attempts to purify the various fractions by selective extraction with ethyl acetate (cf. Windaus, *loc. cit.*) failed, and the combined material was dissolved in much benzene, transferred to a column of silica gel, and eluted with benzene. Concentration of the faintly yellow eluate afforded a mixture of colourless plates and needles, which was separated by fractional crystallisation from benzene–methanol into (i) benzamide, m. p. and mixed m. p. 127°, and (ii) *N*-benzoylcolchide (0·143 g.), micro-m. p. 236° (Windaus gives m. p. 239°). Final elution of the column with methanol gave a brown residue (1·237 g.) recoverable from the eluate, but attempts to purify this material or, to obtain from it crystalline hydrolysis products were unsuccessful.

The manganese dioxide was added to the aqueous concentrates, and the acidified mixture was clarified by a stream of sulphur dioxide before being extracted with chloroform. The extract was washed with 2% sodium carbonate (which removed resinous acidic material; 1·805 g.), dried, and concentrated. A solution of the residue (2·3 g.) in benzene was separated on silica gel into an upper bright yellow section (brown in ultra-violet light) and a lower colourless section (yellow in ultra-violet light). Separate elution with benzene, followed by concentration, gave: (i) colourless rectangular plates (0·040 g.) probably of *N*-benzoylcolchinic acid (arising from incidental hydrolysis) since they melted and effervesced at 182° with formation of the anhydride and were also formed from the anhydride by dissolving the latter in alkali and acidifying the solution; (ii) yellow rectangular plates (1·432 g.) of *N*-benzoylcolchinic anhydride, m. p. 194—195°; and (iii) unidentified stout prisms of micro-m. p. 201°, which were soluble in hot alkali.

Deaminocolchide and Colchide Picrate.—A solution of *N*-benzoylcolchide (0·078 g.) in 95% ethanol (3·5 c.c.) and concentrated hydrochloric acid (3 c.c.) was heated under reflux for 6 hours. The ethanol was distilled off and water (3 c.c.) was added. After 24 hours the precipitate was collected and shaken with ether, unchanged *N*-benzoylcolchide (0·027 g.) remaining undissolved (and being re-treated). Deaminocolchide (0·014 g.), micro-m. p. 130° (from aqueous ethanol) (Windaus gives m. p. 138°), was recovered from the ethereal solution and was slightly augmented by material recovered from an alkali-washed ethereal extract of the aqueous mother-liquor. Concentration of the aqueous mother-liquor and addition of aqueous picric acid gave colchide picrate, micro-m. p. 160—161° (Windaus gives m. p. 165°). Anomalous hydrolysis results were obtained in one experiment where, instead of deaminocolchide, colourless crystals of micro-m. p. 153—155° (from aqueous ethanol) were isolated. This substance was distinct from the oxidation product, micro-m. p. 157°, of *N*-benzoyltrimethylcolchicinic acid and it was not again encountered.

Hydrogenation.—A solution of deaminocolchide (3·59 mg.) in acetic acid (4 c.c.) in presence of palladium black absorbed 0·310 c.c. of hydrogen at 18·8°/751 mm., corresponding to 1·03 double bonds. The product, recovered from the acetic acid solution, formed colourless prisms of micro-m. p. 79—81° from aqueous ethanol.

N-*Acetylcolchinic Anhydride.*—(*a*) A solution of colchiceine (2 g.) in 3% potassium hydroxide (25 c.c.) was treated during 9 hours at 0° with 4% aqueous potassium permanganate (150 c.c.). After a further 12 hours the mixture was acidified, sulphur dioxide was passed in to dissolve the manganese dioxide, and the whole was extracted with chloroform. The brown gum recovered from the chloroform was extracted with benzene, the solution was passed through a column of silica gel, and the yellow section of the resulting chromatogram was eluted with benzene. After renewed chromatography, concentration of the yellow eluate afforded a minute quantity of colourless nodules, micro-m. p. 200° (not further examined), mixed with a larger proportion of yellow needle clusters. The latter afforded *N*-acetylcolchinic anhydride, micro-m. p. 184—185° (from ether) (Found: C, 60·15; H, 4·9. Calc. for $C_{18}H_{19}O_7N$: C, 59·9; H, 5·3%) [Windaus, *loc. cit.*, 1911, records (macro-) m. p. 201°].

(*b*) A solution of *N*-acetylcolchinol (0·4 g.) in 3% potassium hydroxide (6 c c.) was titrated at 20° in the course of 48 hours with 4% potassium permanganate (23·8 c.c.). Discharge of the permanganate colour, at first rapid, was later very slow. The manganese dioxide was filtered off and washed with hot water and then with boiling ethanol, the washings being concentrated and added to the main filtrate, which was then acidified and extracted with chloroform. The recovered brown gum was dissolved in benzene–chloroform (1 : 1), and the solution was passed through a short column of silica gel, from which the yellow eluate on evaporation afforded clusters of yellow needles, micro-m. p. and mixed m. p. with the product from (*a*) 184—185°.

We are glad to acknowledge our indebtedness to Messrs. Imperial Chemical Industries Limited (Dyestuffs Division) for making it possible for one of us (T. Y. J.) to take part in this investigation, to the Royal Society and the Chemical Society for grants for the purchase of colchicine, and to Messrs. Roche Products, Limited, for the gift of a sample of colchicine. Microanalyses were carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW.

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104. *The Low-temperature Polymerisation of* iso*Butene. Part II.**

By P. H. PLESCH.

The polymerisation of *iso*butene in hexane solution by titanium tetrachloride with water and trichloroacetic acid as co-catalysts was investigated at temperatures between −90° and 0°, by an adiabatic technique. The kinetic data, which are of a preliminary nature, show that the reaction is of the first order with respect to the co-catalyst. There are indications that the activation energy of chain initiation is probably less than 4 kcals./mole and that the activation energy of chain termination may be as high as 10 kcals./mole. This is interpreted in terms of the rearrangement of the ion pair at the growing end of the polymer chain when termination takes place. Analytical data indicate that the co-catalyst may be built into the end of the chain at termination. The polarised-molecule theory is shown to be inapplicable to this system, and the carbonium ion theory is developed. The S-shaped reaction curves obtained under certain conditions are explained in terms of a slow build-up of the concentration of growing chains.

THE polymerisation of *iso*butene at low temperatures by Friedel–Crafts catalysts has been the subject of numerous investigations, which have been reviewed recently (Heiligmann, *J. Polymer. Sci.*, 1949, **4**, 183; Plesch, ***Research***, 1949, **2**, 267; *Proc. Roy. Dublin Soc.*, Symposium on Friedel–Crafts Polymerisations, in the press). In this laboratory we have mainly used titanium tetrachloride as catalyst (Plesch, Polanyi, and Skinner, *J.*, 1947, 257, who quote also Seymour, Thesis, Manchester, 1943; A. G. Evans *et al.*, *Nature*, 1946, **157**, 102; Plesch, *Nature*, 1947, **160**, 868) and the outcome of the early work with this halide and of parallel work with boron trifluoride (Evans, *loc. cit.*; A. G. Evans, Meadows, and Polanyi, *Nature*, 1947, **160**, 869; Evans and Polanyi, *J.*, 1947, 252; Evans and Meadows, *J. Polymer Sci.*, 1949, **4**, 359) was the conclusion that in these reactions a third component, called the co-catalyst, was essential. It was found that atmospheric moisture acted as such a co-catalyst. The reactions by means of which this effect was investigated at low temperatures were carried out adiabatically in hexane solution and were followed by recording the temperature rise caused by the heat of polymerisation.

When the reaction was initiated by passing a brisk stream of moist air through a non-reacting solution of *iso*butene and titanium tetrachloride in hexane, the reaction curves (time–temperature plots) were always S-shaped (Plesch, Polanyi, and Skinner, *loc. cit.*, Figs. 3 and 4). Frequently it was found that a given dose of moist air would induce a reaction which would cease before all the monomer had been consumed. In such cases a second dose of moist air would induce a further reaction (*loc. cit.*, Fig. 4). Although the detailed course of the reactions was not reproducible, an examination of the temperature dependence of the initial and maximum rate of reaction showed a certain regularity, as can be seen from Figs. 1 and 2 below. These results suggest that the rate of the polymerisation co-catalysed by water vapour has a positive temperature coefficient. This is the direct opposite of what had been found in our rough preliminary experiments (*loc. cit.*) and by other workers (*e.g.*, Thomas *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 276; Waterman *et al.*, *Rec. Trav. chim.*, 1934, **53**, 699). An explanation of this will be suggested in the Discussion below.

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* Part I, *J.*, 1947, 257.

Although the discovery of the rôle of water in these polymerisations had made clear at least one of the possible causes of the irreproducibility, which seemed to characterise the polymerisation of *iso*butene, the deliberate use of water vapour as co-catalyst had not lead to any appreciable degree of reproducibility in these reactions. The reasons for this are not difficult to find.

Water vapour introduced into a hydrocarbon solution at a temperature far below 0° must form a dispersion of ice and therefore its action could not be envisaged as anything but heterogeneous. This view was supported by the milky appearance of the final polymer solution. Even if the water had been initially in a molecularly disperse form in the reaction mixture it must be presumed that the titanium tetrachloride–water complex which is postulated as the real initiator of the reaction (Plesch, Polanyi, and Skinner, *loc. cit.*) would not be soluble in the mixture of *iso*butene and hexane and would tend to form aggregates. Thus the rate and extent of reaction would depend on the size and number of these aggregates and on the rate at which they settled out on the walls and fittings of the reaction vessel.

FIG. 1.

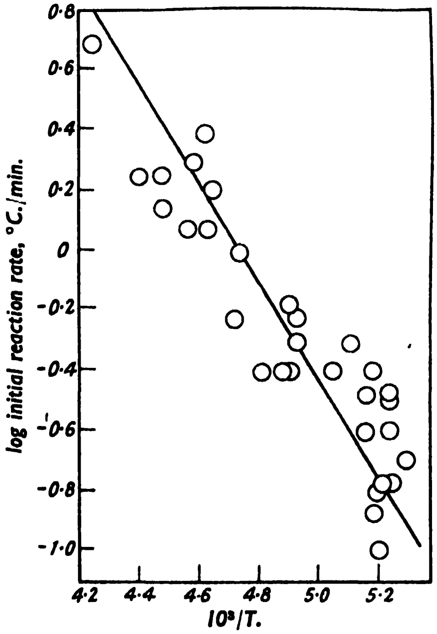


FIG. 2.

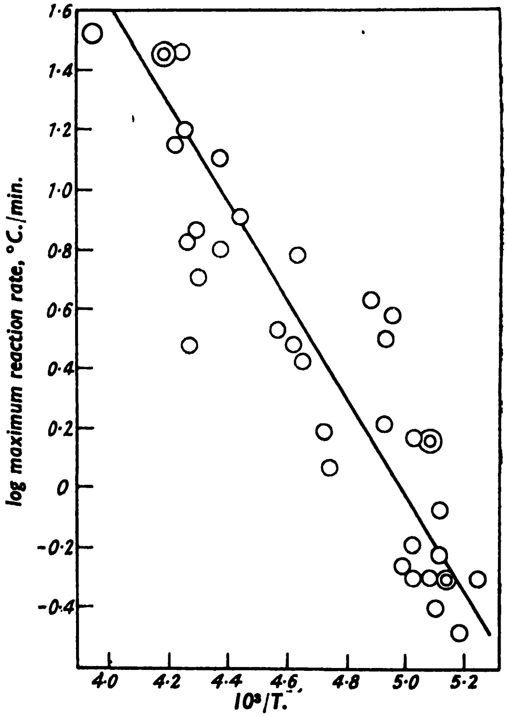


FIG. 1.—*Adiabatic polymerisation of* isobutene *(2·5 moles/l.) by* $TiCl_4$ *(4·8 × 10^{-3} mole/l.), co-catalysed by water vapour. Initial rate as a function of temperature.*

FIG. 2.—*Maximum rate as a function of temperature. Otherwise as for Fig.* 1.

For these reasons we attempted to find a co-catalyst which would make it possible to carry out the reaction under homogeneous conditions. We required a co-catalyst which would be soluble in a hydrocarbon medium and whose complexes with titanium tetrachloride would also be soluble in such a medium. It was evident that no inorganic substance was likely to fulfil both these conditions. Investigations in these laboratories running parallel to the work reported here had shown that acetic acid (Evans, Meadows, and Polanyi, *loc. cit.*) and *tert.*-butanol (Evans and Polanyi, *loc. cit.*) are capable of acting as co-catalysts to boron trifluoride in the polymerisation of gaseous *iso*butene at room temperature, but neither of these substances was found to be effective as co-catalyst to titanium tetrachloride in the low-temperature polymerisation of *iso*butene (Plesch, *Nature*, 1947, **160**, 868). On the contrary, they were found to act as inhibitors to this reaction. Diethyl ether and ethanol have been reported previously (Plesch, Polanyi, and Skinner, *loc. cit.*) to have a similar inhibiting effect.

The Present Investigation.

Qualitative Results. The Survey of Co-catalysts.—The qualitative results of the search for co-catalysts other than water are presented in Table I. According to our views on the nature of this polymerisation, a substance, in order to act as co-catalyst, must be capable of forming with the catalyst a complex which is a sufficiently strong acid to donate a proton to the monomer, thus converting it into a carbonium ion. It is well known that concentrated sulphuric acid will polymerise *iso*butene to a product of low molecular weight at room temperature, but we found that it would not do so at low temperatures. We thought that possibly sulphuric acid might form with the titanium tetrachloride a complex acid strong enough to initiate polymerisation at low temperatures, though of course such a complex could not be expected to be soluble in hexane. Experiment showed that concentrated sulphuric acid did indeed act as a very potent co-catalyst at −80°. Since the effect might have been due to the water contained in the sulphuric acid, 20% oleum which could not contain any water was tried and was found to be as effective as sulphuric acid. The reactions co-catalysed by sulphuric acid were very violent and virtually complete, and the product was of relatively low molecular weight, probably not above 20,000.

Table I.

T_0.[a]	*iso*Butene concn., mols./l.	$TiCl_4$ concn., 10^{-2} mols./l.	Test substance, X.	Concn. of X, millimols./l.	Effect.
−87°	2	4·8	Conc. H_2SO_4	50	Vigorous polymn.
−86	2	0	,, ,,	50	No polymn.
−79	2	4·8	20% oleum	50	Vigorous polymn.
−68	2	4·8	,,	50	,,
−79	2	0	,,	50	No ,,
−25 to −120	0·62 to 2·5	0·2 to 5	$CCl_3{\cdot}CO_2H$ in hexane	0·25 to 6·5	Polymn.
−75	1·25	4·8	$CHCl_2{\cdot}CO_2H$ in hexane	1·9 9·5[c]	Slight indication of polymn.; poisoning[b]
−75	1·25	4·8	$CH_2Cl{\cdot}CO_2H$ in hexane	$>1{\cdot}0$[d]	No polymn.; poisoning
−62	2·5	2·4	$CH_3{\cdot}CO_2H$ in hexane	0·85	No polymn.; poisoning
−60	2·5	2·4		0·85	
−76	2·5	2·4		8·5	
+20	2·5	2·4		8·5	

[a] T_0 is the temperature of the reaction mixture when X was added. [b] " Poisoning " means that the addition of trichloroacetic acid or water vapour to a reaction mixture to which the reagent X had been added previously, caused no reaction, or only at a rate much smaller than that in the absence of X. [c] Two separate additions of this acid to the same reaction mixture were made. [d] An emulsion of the (liquid) acid in hexane was used.

Since it was thought that other strong acids might act in a similar manner, trichloroacetic acid was tried, and was indeed found to possess a strong co-catalytic activity. Its acid strength in water is of the same order as that of sulphuric acid and it has the advantage for the present purpose of being appreciably soluble in hexane even at −80°. The complexes which it forms with titanium tetrachloride also appear to be soluble in hexane. The main part of this paper is devoted to the results of polymerisation studies carried out with this co-catalyst.

Experimental.

Purification of Reagents.—*Hexane.* Commercial hexane was purified by standard methods; it was distilled from phosphoric oxide through a 3-ft. point column, and the fraction distilling between 67·5° and 68·5° was collected. It was stored over phosphoric oxide until introduced into the reservoir attached to the polymerisation apparatus.

Titanium tetrachloride. The commercial product was distilled in a stream of dry air until the intensity of the pale yellow colour could not be reduced by further fractionations. A weighed quantity was dissolved in the calculated quantity of pure dry hexane in the absence of atmospheric moisture, to give a 0·6M-solution (approx. 12% w/v). It was prepared in batches of about 200 ml. and stored in a reservoir connected to the polymerisation apparatus. The solution was almost colourless, clear, and free from deposit even after several months' storage. The colour of the titanium tetrachloride was caused by traces of iron and chromium.

iso*Butene.* This was a much appreciated gift from Messrs. I.C.I. (Billingham) Ltd., and was stated to be 99% pure. Before use it was distilled *in vacuo* from about −80° to liquid-air temperature until the liquid was perfectly clear and free from white flocks. For the experiments an amount of *iso*butene approximately equal to that required was collected in a roughly graduated trap, and the exact amount determined by weighing.

Trichloroacetic acid. The commercial, pure but deliquescent product was crystallised 4 times from hexane, and then dissolved in hexane to give an approx. N/10-solution. This was stored over phosphoric oxide and its strength was determined by titration. Such solutions could be thus stored for several weeks without undergoing change in concentration.

Apparatus and Technique.—The apparatus and technique used in the present series of polymerisation experiments were essentially the same as those previously described (Plesch, Polanyi, and Skinner, *loc. cit.*) which had been used for studying the co-catalytic effect of water vapour. The quantities of hexane, *iso*butene, and catalyst solution were always so adjusted that the volume of the whole batch was 200 ml. at room temperature.

The reaction was started by adding to the non-reacting solution of *iso*butene and titanium chloride in hexane a measured quantity of the co-catalyst solution from a pipette through an opening in the stopper of the reaction vessel. It was ascertained by control experiments that the amount of atmospheric moisture admitted to the reaction vessel during this addition of the co-catalyst was insufficient to cause measurable reaction.

The progress of the reaction was observed by noting the temperature of the reaction mixture on a pentane thermometer at definite time intervals. Since the polymerisation of *iso*butene is exothermic by more than 10 kcals./mole, the temperature changes accompanying this reaction provide an accurate and sensitive means of observation. For instance, the complete polymerisation of 7 g. of *iso*butene (0·125 mole) in 190 ml. of hexane gave a temperature rise of 14° in our apparatus.

At the end of the reaction 2—3 ml. of 90% ethanol were added to the polymer solution. This removed the catalyst by precipitating it as a pale yellow oil, leaving a clear and colourless solution of poly*iso*butene in hexane.

Measurement of Molecular Weight.—The mean molecular weight of the poly*iso*butene specimens obtained in the course of this work was calculated from the intrinsic viscosities of their solutions in hexane, by means of the formula (Houwink, *J. pr. Chem.*, 1940, **157**, 15) $[\eta] = KM^{a}$, where $[\eta]$ is the intrinsic viscosity, M is the mean molecular weight, and K and a are constants.

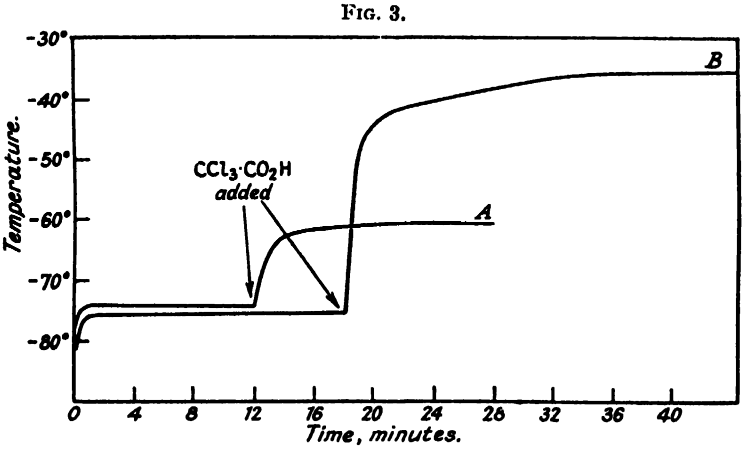
The intrinsic viscosity of the unfractionated polymer was determined as follows: After reaction a small portion of the mixture discharged from the reaction vessel was made up into an approx. 1% w/v solution in hexane, and this was diluted, *e.g.*, to $\frac{1}{2}$, $\frac{1}{4}$, and $\frac{1}{8}$. The flow times of not less than three such solutions were measured in the usual manner in a B.S.S. 188 No. 1 U-tube viscometer at 25°, and from it and the flow time of the pure solvent the specific viscosity $\eta_{sp.}$ was calculated. After the timing, the content of the viscometer was weighed in a tared weighing-bottle, dried to constant weight (16 hours at 90—110°), and re-weighed. Hence the concentration c of the polymer was found. The plot of $\log (\eta_{sp.}/c)$ against c, extrapolated to $c = 0$, gave the intrinsic viscosity $[\eta]$, from which the molecular weight was calculated by the above formula, with $K = 3{\cdot}6 \times 10^{-4}$ and $a = 0{\cdot}64$. As these constants had been obtained by Flory (*J. Amer. Chem. Soc.*, 1943, **65**, 372) for solutions of poly*iso*butene in di*iso*butene it was ascertained by experiment that there was no significant difference between the intrinsic viscosities of poly*iso*butene in this solvent and in hexane.

Duplicate determinations of the molecular weights obtained in this way agree to within 5%, but their relation to the true weight-average and number-average molecular weights is somewhat doubtful, as the measurements were carried out on unfractionated specimens, whereas the constants in the formula had been obtained from measurements on carefully fractionated polymer samples.

POLYMERISATION WITH TRICHLOROACETIC ACID AS CO-CATALYST.

General.—The polymerisation of *iso*butene by titanium tetrachloride and trichloroacetic acid has been studied under a variety of conditions. It was found that the polymerised solutions were always much less opaque than those which had been produced with water vapour as co-

FIG. 3.

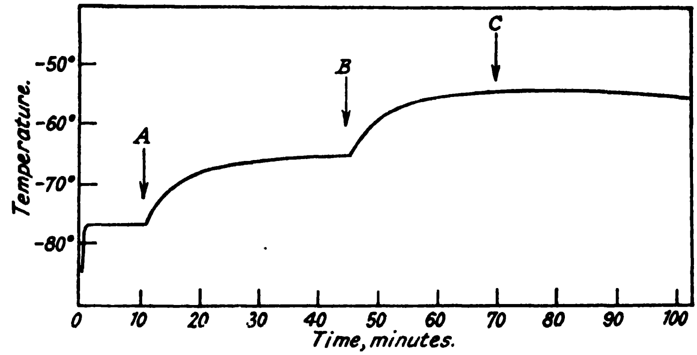


Adiabatic polymerisation of isobutene. *Typical time–temperature curves. Catalyst:* $TiCl_4$ (48 *millimoles/l.*). *Concn. of* isobutene *:* A 2·5, B 0·62 *mole/l. Concn. of* $CCl_3{\cdot}CO_2H$: A 1·65, B 3·3 *millimoles/l. Catalyst added at time* = 0.

catalyst, and the orange-red crystalline sediment, which had always been present when water was used, was absent from the solutions polymerised with trichloroacetic acid.

Whereas the curves showing the progress of reaction with time (time–temperature curves) obtained with water-vapour co-catalysis were always S-shaped, the rate of the reactions induced by trichloroacetic acid decreased monotonically from the start, provided that the molar ratio titanium tetrachloride/trichloroacetic acid was greater than about 4 (for starting temperatures near −80°) (Figs. 3 and 4). For reactions in which this ratio was less than 4, the time–temperature curves became the more pronouncedly S-shaped, the lower the value of this ratio (see Fig. 5).

FIG. 4.



Adiabatic polymerisation of isobutene *in hexane solution by* $TiCl_4$ *and* $CCl_3\cdot CO_2H$. *Concn. of* isobutene, 10% (*v/v*, i.e., ~0·25 *mole/200 c.c.*), *and of* $TiCl_4$, 1% (*w/v*, i.e., $9\cdot8 \times 10^{-3}$ *mole/200 c.c.*). *The* $TiCl_4$ *was added at* t = 0. *The quantities of trichloroacetic acid added were at* A $6\cdot6 \times 10^{-5}$ *mole*, B $3\cdot3 \times 10^{-4}$ *mole, and at* C $6\cdot6 \times 10^{-4}$ *mole*.

FIG. 5.

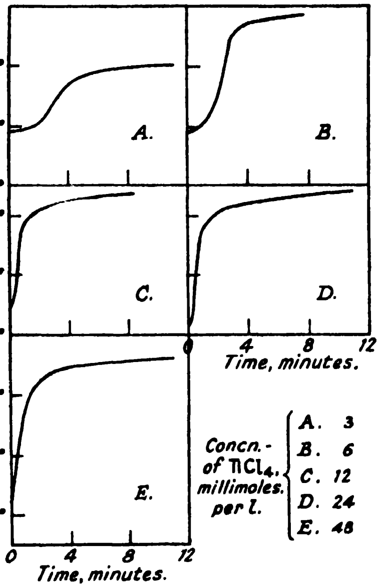


FIG. 6.

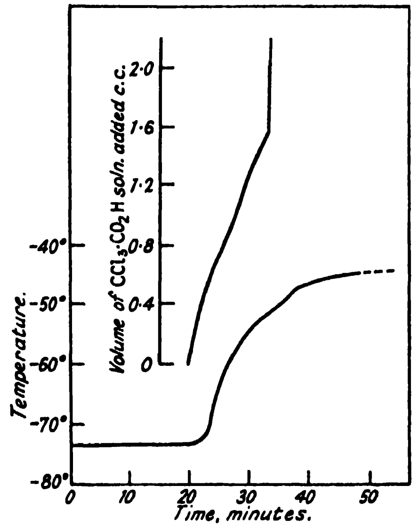


FIG. 5.—*The effect of varying the catalyst : co-catalyst ratio. Concn. of* isobutene 1·25 *mole/l. Concn. of* $CCl_3\cdot CO_2H$ 3·3 *millimoles/l.*

FIG. 6.—*Slow addition of a solution of* $CCl_3\cdot CO_2H$ ($1\cdot2 \times 10^{-2}$ *mole/c.c.*) *in hexane to* 200 *c.c. of* isobutene *solution* (1·25 *moles/l.*) *containing* $4\cdot8 \times 10^{-2}$ *mole/l. of* $TiCl_4$.

The shape of the time–temperature curve is also influenced by the rate at which the co-catalyst is added to the reaction mixture. By adding it at a small and constant rate, S-curves can be produced even in the presence of excess of catalyst (see Fig. 6).

When the co-catalyst is added at the usual very high rate, *e.g.*, 1 ml. in less than 5 seconds in the presence of excess of catalyst, the reaction rate is greatest at the very start of the reaction. Although temperature readings were taken every 15 seconds, the finite time required for the co-catalyst to enter the mixture—even when this is well stirred, as it always was—introduced a considerable error into the determination of the maximum reaction rate when this was given by the temperature rise during the first 15 seconds from the addition of the co-catalyst.

The reproducibility of the maximum reaction rate was much greater than in the experiments carried out with water as co-catalyst. The reproducibility decreased as this rate increased, a feature which can be accounted for in terms of the finite time of mixing discussed above, and of the experimental difficulties and inaccuracies. Even in cases where the maximum (initial) rates were in close agreement, the later course of the reactions was not exactly reproducible so that the extent of reaction and the time required for the reaction to cease were variable for a given set of conditions.

FIG. 7.

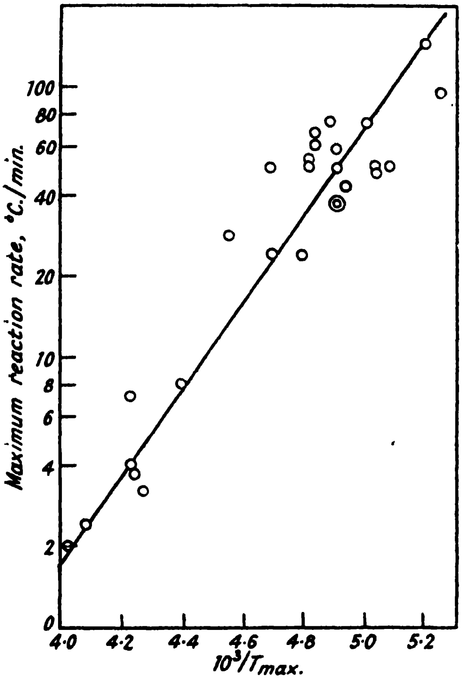


FIG. 8.

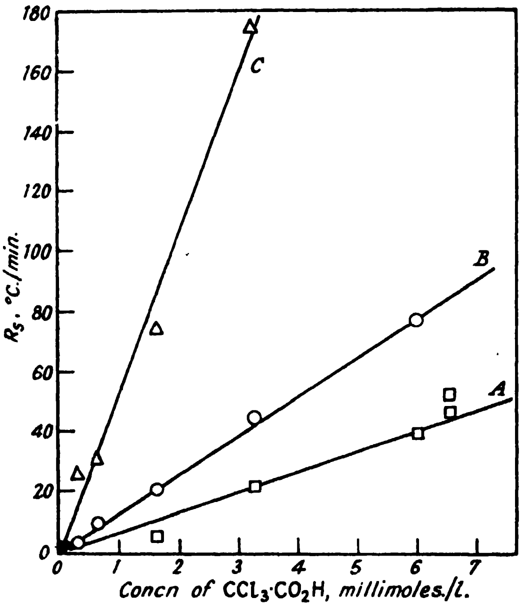


FIG. 7.—*The maximum reaction rate as a function of temperature.* iso*Butene concn.* 1·25 *moles/l.*, $TiCl_4$ *concn.* 4·8 × 10^{-3} *mole/l.* $CCl_3{\cdot}CO_2H$ *concn.* 6 × 10^{-3} *mole/l.*

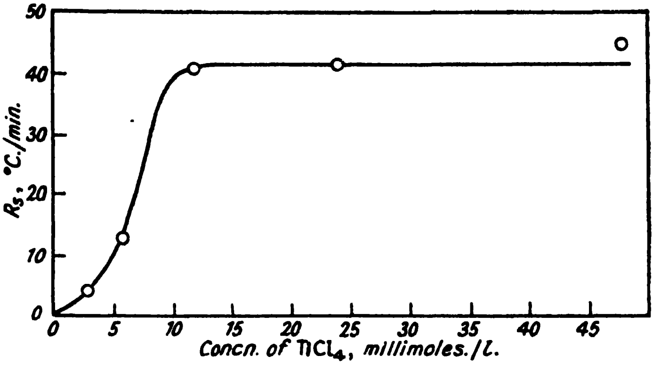
FIG. 8.—*The standardised maximum reaction rate* R_s *as a function of co-catalyst concn. for three* isobutene *concns.* : A 0·62, B 1·25, C 2·5 *moles/l.* $TiCl_4$ *concn.* 48 *millimoles/l.*

The reproducibility of the molecular weights was considerably greater than in the experiments with water co-catalysts. The sensitivity of the molecular weight to temperature and to monomer concentration is probably responsible for the degree of irreproducibility remaining in the present experiments.

The kinetic results to be presented below must be regarded as preliminary for the reason that they were obtained from adiabatic experiments. None the less they provide some new information about the mechanism of this polymerisation. In the present investigations we have determined the influence of the concentrations of *iso*butene, titanium tetrachloride, and trichloroacetic acid, and of the starting temperature of the reaction, on the maximum reaction rate and the molecular weight.

Variation of the Maximum Reaction Rate with Temperature.—The logarithm of the maximum reaction rate was plotted against the reciprocal of the absolute temperature $T_{max.}$ at which the maximum rate occurred (Fig. 7). In very fast reactions this was not very well defined. For all the experiments represented in Fig. 7 the *iso*butene concentration was 1·25 moles/l. (10% v/v) and the catalyst (titanium tetrachloride) and co-catalyst (trichloroacetic acid) concentrations were 4·8 × 10^{-3} and 6 × 10^{-3} moles/l. respectively (1% and 0·5% w/v respectively). These results indicate a negative "activation energy" of about −7·5 kcals./mole for the over-all reaction.

FIG. 9.



R_s *as a function of the* TiCl₄ *concn.* iso*Butene concn.*, 1·25 *moles/l.* CCl₃·CO₂H *concn.*, 3·3 × 10^{-3} *mole/l.*

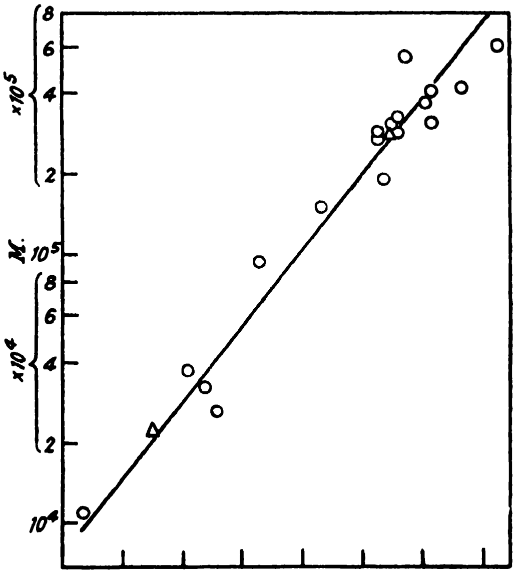
Effects of the Concentrations of the Three Reactants on the Maximum Reaction Rate.—While studying these effects it was impossible to adjust conditions in such a manner that the maximum rate always occurred at the same temperature. For this reason the observed maximum rate occurring at an absolute temperature $T_{\text{max.}}$ was adjusted to the fixed standard temperature −75° by means of the "activation energy" of −7·5 kcals./mole reported above. In this way the standardised maximum reaction rates R_s were obtained.

Variation of R_s *with Co-catalyst Concentration.*—This is shown in Fig. 8 for three different concentrations of *iso*butene. In these experiments the titanium tetrachloride concentration was constant at 4·8 × 10^{-3} mole/l. and the temperatures at which the maximum reaction rate occurred were in the region −70° to −85°. R_s is seen to increase linearly with the co-catalyst concentration.

Owing to the uncertainties inherent in the experimental method the slopes of the lines shown in Fig. 8 should not be considered as more than a first approximation. The ratios of these slopes indicate that the polymerisation is probably of an order greater than unity with respect to *iso*butene, but it would not be justifiable to attempt an evaluation of the exact order from the present data.

Dependence of the Standardised Maximum Reaction Rate R_s ***on the Titanium Tetrachloride Concentration.***—For constant *iso*butene and co-catalyst concentrations, this dependence is shown in Fig. 9. Beyond a certain point the rate appears to be independent of the catalyst concentration.

FIG. 10.



The mean mol. wt. of the polymer as a function of the mean absolute temperature during the reaction. iso*Butene concn.* 1·25 *moles/l.* CCl₃·CO₂H *concn.* 3·3 *millimoles/l.* TiCl₄ *concn.* 48 *millimoles/l.* (○). 24 *millimoles/l.* (△).

Yield of the Polymerisation.—For a fixed catalyst concentration of 4·8 × 10^{-3} mole/l. the polymerisation of a 5% v/v solution of *iso*butene goes to at least 90% completion for T_0 (the starting temperature) in the region of −75°, provided that the trichloroacetic acid concentration is greater than about 1·2 × 10^{-3} mole/l. For higher concentrations of *iso*butene the yields were not reproducible, probably in consequence of the high viscosity of these solutions.

Effect of Temperature on the Molecular Weight of the Polymer.—In Fig. 10 the logarithm of the molecular weight is plotted against the reciprocal of the mean temperature T_m during the experiment. T_m is the arithmetic mean between the starting temperature T_0 and the final temperature of the reacted solution at the end of the polymerisation.

TABLE II.

The variation of molecular weight with monomer and co-catalyst concentration.

In all the experiments recorded in this table the titanium tetrachloride concentration was 4·8 × 10^{-3} mole./l.

Expt. no.	$-T_m$.	Concn. of *iso*butene, mols./l.	Concn. of $CCl_3\cdot CO_2H$, millimol./l.	Observed mol. wt. (M) $\times 10^{-3}$.	M_s $\times 10^{-3}$.	Mean M_s $\times 10^{-3}$.
154	60°	1·25	0·66	286	950	600
158	74			250	280	
159	73			460	550	
151	70	1·25	1·65	420	640	800
152	61			325	1000	
156	58			190	750	
149	60	1·25	3·3	305	1000	840
153	61			280	880	
177	65			370	840	
181	66			310	650	
150	66			400	820	
155	58	1·25	6·6	270	1000	—
157	62			580	1600	
178	60			280	950	
166	69	0·62	1·65	430	720	—
164	68		3·3	280	500	
165	68		6·6	285	500	
167	69		6·6	240	400	
163	61	2·5	0·33	400	1250	—
161	55		1·65	280	1350	
162	56		3·3	255	960	

TABLE III.

Specimen no.	Co-catalyst	Mol. wt.[a] $\times 10^{-3}$.	Found.[b]			Calc.[c]
			C, %.	H, %.	Cl, %.	Cl, %.
121	H_2O	20	—	—	0	0
119	,,	22	—	—	0	0
77	,,	243	85·2	14·4	0	0
206.I[e]	$CCl_3\cdot CO_2H$	11	—	—	1·7 2·1	1·0
206.II[f]	,,	11	—	—	0·2 0·6	1·0
189	,,	22·4 28[d]	—	—	0·2 0·7	0·48
194.I	,,	26	85·2 85·1	12·6 14·2	0·3	0·4
194.II	,,	26	85·3 85·3	14·0 14·2	0·3	0·4
156	,,	190	85·5	14·5	0	0·056

[a] Molecular weight before precipitation of the polymer. [b] Micro-analyses by Messrs. Weiler and Strauss, Oxford, England. [c] Assuming the presence of one trichloroacetate group per molecule. [d] Molecular weight after two precipitations. [e] Reaction mixture washed three times with distilled water, dried, and evaporated in a high vacuum. [f] Reaction mixture precipitated in methanol–acetone mixture, washed with acetone, and evaporated in a high vacuum.

Effects of the iso*Butene and Co-catalyst Concentrations on the Molecular Weight.*—Table II records results showing these effects. Since the mean temperature during the polymerisation has such a great effect on the molecular weight, the measured values of the molecular weight (M) were adjusted to the standard temperature −75° by means of T_m, the mean temperature during the reaction, and the relation between T_m and M is represented in Fig. 10. The standardised molecular weights thus obtained are designated by M_s.

It is seen from the table that M_s shows only a slight increase with the co-catalyst concentration but that it increases with the *iso*butene concentration. In view of the uncertainties involved in the calculation of the M_s values, and considering that these refer to the mean molecular weight of the end-product of the reaction, it would not be justifiable to draw any definite conclusions from these data as to the exact relationship between the molecular weight and the monomer concentration.

Analysis of the Polymer.—A certain number of polymer samples were analysed for chlorine. The main practical difficulty was to make sure that the polymer was free from trichloroacetic acid and from hydrolysis products of titanium tetrachloride.

The polymer solutions were freed from titanium tetrachloride by adding 2—3 ml. of ethanol to the solutions at the end of the reactions. This reacted with the titanium tetrachloride, and the product separated as a yellow oil. The polymer was then precipitated in a large excess of 90% ethanol and the visco-elastic mass of polymer was well kneaded in a fresh batch of ethanol. It was then dissolved in hexane to give an approx. 20% solution, precipitated again in ethanol, kneaded in ethanol, and again dissolved in hexane. The solution was then evaporated *in vacuo* at room temperature. When the bulk of the hexane had been removed, evacuation by way of a liquid-air trap was continued for 24 hours, at a pressure less than 10^{-3} mm. Hg. The colourless and transparent polymer thus obtained was used for analysis. The results of the analyses are shown in Table III. In one case (No. 194) the original polymer solution was divided into two portions, one of which (194.I) was precipitated in boiling water and the polymer so obtained dissolved in hexane and then precipitated in ethanol and thereafter treated as described. The second portion (194.II) was treated in the usual way with two ethanol precipitations. There is no difference between the chlorine contents of these two specimens. The absence of chlorine from specimens 119 and 121 which were prepared by water co-catalysis shows that where any chlorine was found in the polymers it could not have originated from end-groups derived from the catalyst. This is further supported by the absence of an incombustible residue. The absence of chlorine from the specimens 77 and 156 rules out the possibility of physical entrainment of chlorine compounds in polymer micelles, since this effect would be much greater in polymers of higher molecular weight. The precipitation process necessarily removes some of the fractions of lowest molecular weight (this is shown in specimen 189) and thus it is understandable that the measured chlorine content of the polymers is slightly less than that to be expected from the molecular weight determined before precipitation.

The data presented in Table III thus indicate that chlorine is present only in the polymer when trichloroacetic acid was used as co-catalyst.

Discussion.

The Mechanism of the Polymerisation.—The mechanism of the polymerisation of *iso*butene by Friedel–Crafts catalysts is now believed to involve reaction between carbonium ions and monomer. The original carbonium-ion theory of Whitmore (*Ind. Eng. Chem.*, 1934, **26**, 94), Hunter and Yohe (*J. Amer. Chem. Soc.*, 1933, **55**, 1248), and Brunner and Farmer (*J.*, 1937, 1039) was developed by Polanyi and his collaborators (*J.*, 1947, 252, 257) who showed that a co-catalyst, as well as the halide catalyst, was required to bring about polymerisation. This was confirmed by Norrish and Russell (*Nature*, 1947, **160**, 543). It has been shown again in the present work that a co-catalyst is essential for the reaction and therefore the older theories such as those of Price (*Annals N.Y. Acad. Sci.*, 1943, **44**, 368; " Reactions at Carbon-Carbon Double Bonds " New York, 1946) and Eyring and his collaborators (*Annals N.Y. Acad. Sci.*, 1943, **44**, 382), which ignored this, cannot apply to the systems investigated by us.

According to our present views, the initiating species is a complex between catalyst and co-catalyst, which is formed by the reaction (I) shown in the scheme below.

The complex is thought to react with a molecule of monomer according to reaction (II) in which XA^-H^+ represents the complex ion pair. This is the initiation step which involves the transfer of a proton from the catalytic complex to a molecule of monomer.

The propagation of the polymerisation is believed to take place by the combination of the carbonium ion formed in the initiating step with a molecule of the monomer, with transference of the charge to the end of the chain thus formed (Polanyi and his collaborators, *loc. cit.*). This is represented in reaction (III). In the previous attempts at formulating the propagation mechanism, the question of the fate of the anion was left open. It is clear, however, that in the system under consideration the anion cannot be separated to any considerable distance from the carbonium ion. If one uses the method of Fuoss and Kraus (*J. Amer. Chem. Soc.*, 1933, **55**, 1019) to calculate the degree of dissociation of the ion pair

$$\text{-CH}_2\cdot(\text{CH}_3)_2\text{C}^+\cdot(\text{Cl}_3\text{C}\cdot\text{CO}_2\cdot\text{TiCl}_4)^-$$

in hexane at −80°, one obtains a value of the order of 10^{-22}. Therefore in the course of chain propagation the anion must remain in the vicinity of the carbonium-ion end of the growing polymer chain. A. G. Evans and Meadows (*J. Polymer Sci.*, 1949, **4**, 359), approaching the problem in a rather different manner, reached the same conclusion. This is an additional reason why the older theories (Price, *loc. cit.*; Eyring, *loc. cit.*; Heiligmann, *J. Polymer Sci.*, 1949, **4**, 183) which involve considerable charge separation cannot be applicable to this system.

The termination of the chains could take place by several different mechanisms : The ion pair at the growing end of the polymer chain may undergo a unimolecular rearrangement to give an ester (or alcohol if the co-catalyst is water) (Norrish and Russell, *loc. cit.*) as shown in reaction (IV*a*). In this case the halide will remain co-ordinated on to the oxygen of the terminal group. It will only be removed by treating the polymer with, *e.g.*, water which can break up the co-ordination complex. This was shown by Staudinger ("Die hochmolekularen organischen Verbindungen," Berlin, 1932) with polystyrene prepared with stannic chloride as catalyst, and is confirmed by our observation that addition of water to a clear polymerised reaction mixture which had been freed from excess of titanium tetrachloride by the addition of alcohol produced a tenuous but quite definite white precipitate presumed to be titanium oxide.

The suggested mechanism accounts for the consumption of the co-catalyst in the course of the reaction, which is indicated by experiments such as that represented in Fig. 4 and it is supported by the analytical evidence given in Table III.

The formation of *tert.*-butyl trichloroacetate by a bimolecular reaction between monomer and the ion pair, leaving the polymer with a terminal double bond [reaction (IV*b*)], is a possibility which cannot be neglected, especially at higher temperatures. It would also account for the consumption of the co-catalyst.*

The alternative is the loss of a proton from the growing end of the polymer chain, leaving a terminal double bond. This process could take place in three different ways : (*a*) A unimolecular decomposition of the terminal ion-pair in which the catalytic complex is regenerated [reaction (V*a*)]. (*b*) A bimolecular reaction with monomer, leading to chain transfer [reaction (V*b*)]. (*c*) A bimolecular reaction with the terminal double bond of a dead polymer molecule formed by process (IV*b*), (V*a*), or (V*b*) in which the catalytic complex is regenerated as in (*a*) [reaction (V*c*)].

The complete reaction is thus represented by the scheme on following page.

If for the moment the transfer reactions (V) are neglected, the set of differential equations describing this reaction scheme with the termination mechanism (IV*a*) is as set out below.

This is analogous to the schemes used by Eley and Pepper (*Trans. Faraday Soc.*, 1947, **43**, 112; cf. Pepper, *ibid.*, 1949, **45**, 397, and Eley and Richards, *ibid.*, p. 425).

$$-\mathrm{d}[\mathrm{AH}]/\mathrm{d}t = k_0c[\mathrm{AH}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$-\mathrm{d}[\mathrm{CAH}]/\mathrm{d}t = -\frac{\mathrm{d}[\mathrm{AH}]}{\mathrm{d}t} - k_im[\mathrm{CAH}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$-\mathrm{d}m/\mathrm{d}t = k_im[\mathrm{CAH}] + k_pm\mathrm{M}^* \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\mathrm{dM}/\mathrm{d}t = k_t\mathrm{M}^* \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\mathrm{dM}^*/\mathrm{d}t = k_im[\mathrm{CAH}] - k_t\mathrm{M}^* \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Where concentrations are as follows : *m isobutene*, *c* titanium tetrachloride, [AH] trichloroacetic acid, [CAH] initiating complex, M* growing polymer chain, and M dead polymer chain.

If we make the usual stationary state assumption, *i.e.*, put M* = constant, and also assume that k_p and k_t are independent of chain length, we get for the rate of reaction

$$-\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{k_ik_p}{k_t}\,.\,m^2[\mathrm{CAH}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

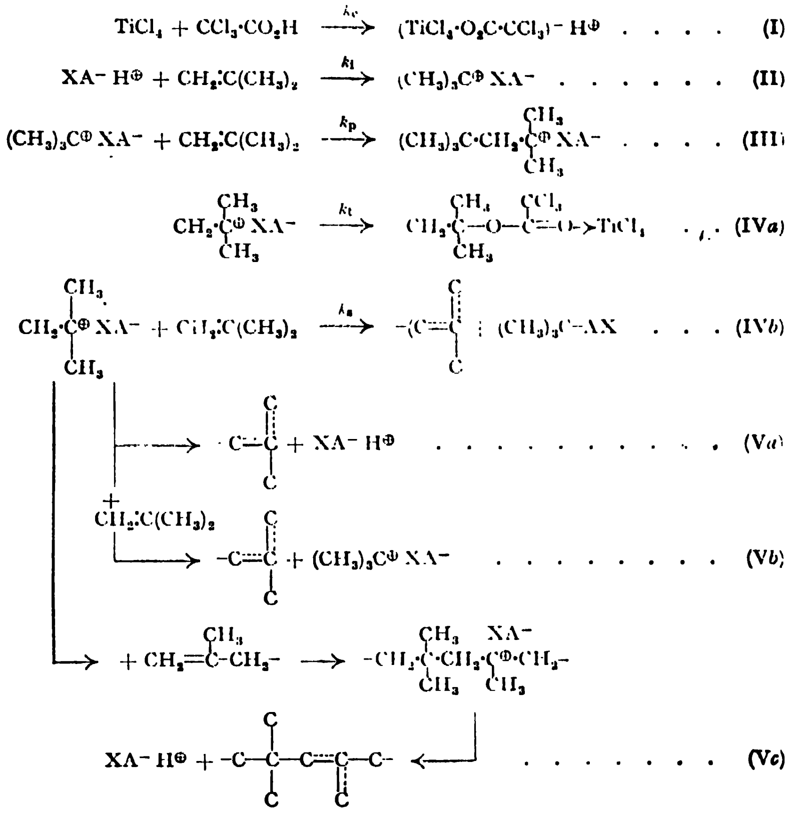
when $k_pm/k_t \gg 1$.

If we make the plausible assumption that reaction (I) goes practically to completion in the presence of excess of titanium tetrachloride, the unknown term [CAH] can be replaced by the known co-catalyst concentration [AH].

---

* *iso*Butene and trichloroacetic acid react rapidly to give the *tert.*-butyl ester (Scovill, Burke, and Lankelma, *J. Amer. Chem. Soc.*, 1944, **66**, 1039).

It is indeed found in the present work that the maximum reaction rate is proportional to the first power of the co-catalyst concentration, but the correlation cannot be regarded as definitely established until isothermal measurements are available. The order of the reaction with respect to monomer cannot be derived unambiguously from the present set of measurements, though it is probably greater than unity.



The dotted lines in this scheme indicate alternative positions for the double bond.

The molecular weight of the polymer is given by

$$M = M^0 m(k_p/k_t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where M^0 is the molecular weight of the monomer. The present data indicate that the molecular weight depends on the monomer concentration and is independent of the co-catalyst concentration; but again the data do not permit one to deduce exactly how the monomer concentration affects the molecular weight.

If termination takes place by reaction (IV*b*) the maximum reaction rate is given by

$$-\mathrm{d}m/\mathrm{d}t = k_i m[\mathrm{CAH}]$$

if $k_p/k_s \gg 2$. The molecular weight is given by

$$M = M^0 k_p/k_s$$

The facts that the observed order of the reaction rate with respect to monomer concentration is between 1 and 2, and that the molecular weight depends on a power of *m* rather less than 1, may indicate that both termination mechanisms (IV*a*) and (IV*b*) play a part in this reaction.

Although the present data on the concentration-dependence of the rate and molecular weight do not provide much information, the temperature dependence of these quantities yields some interesting results. Considering first the reaction with termination (IV*a*), we assume that the number-average molecular weight of the final polymer is given by equation (7), and denote by E_i, E_p, and E_t the activation energies corresponding to the three rate constants. We then find from Figs. 7 and 10 that

$$E(\text{rate}) \equiv E_i + E_p - E_t$$

and

$$E(\text{Mol. wt.}) \equiv E_p - E_t$$

are equal within the limits of accuracy of the present experiments and have a value of $-7{\cdot}5 \pm 2$ kcals./mole.

Thus if the mechanism outlined above is correct we may assign an upper limit of about 4 kcals./mole to E_i, and it may well be very much less than this.

Since there is a great similarity between the initiation and propagation reactions, it is probable that E_p is also a very small quantity. Thus it appears that E_t may well be as high as 6—10 kcals./mole.

The reason for this high activation energy may be found in the drastic rearrangement which must take place in the ion pair during the termination act. In the course of chain propagation the configuration of the anion is probably such that the trichloroacetate residue is co-ordinated symmetrically with both its oxygen atoms to the titanium tetrachloride. When the termination takes place, this symmetrical arrangement is disturbed, and both ions must rearrange themselves so that a covalent bond can be formed between them.

If the termination (IV*b*) applies, a similar argument with E_s in place of E_t leads to the same conclusions about E_i and E_p. The value of E_s estimated in this way is the same as that of E_t. Its interpretation is also the same as that of E_t, since the main difference between termination mechanisms (IV*a*) and (IV*b*) is that the latter involves both the making and breaking respectively of two double bonds of very similar constitution which would hardly affect the energetics of the reaction.

It is necessary to examine more closely the assumption made above, that a stationary state is established during the course of the reactions. There can be little doubt that during the period of maximum rate, whenever it may occur, this is approximately true. But in some reactions (Fig. 5) there was an initial period of acceleration and during this, conditions are not stationary. It may therefore be of interest to discuss the conditions under which S-shaped reaction curves are obtained.

The Origin of the S-Curves.—If we compare the results obtained with water as co-catalyst (Plesch, Polanyi, and Skinner, *loc. cit.*) which were summarised on p. 543 and the results obtained with trichloroacetic acid as co-catalyst, we see that the most striking differences between the two sets of experiments are the different shapes of the curves showing the progress of reaction with time, and the opposite sign of the temperature coefficient of the polymerisation velocity. Whereas the time–temperature curves for reactions co-catalysed by water vapour were invariably S-shaped, those for trichloroacetic acid co-catalysis showed a monotonically decreasing reaction rate unless the concentration of catalyst was smaller than about four times the concentration of co-catalyst. The third condition under which S-curves are obtained is the slow addition of the co-catalyst (Fig. 6). If we ask the question: What is the feature which is common to the different circumstances which give rise to S-shaped curves?, we find that in each case there is a good reason to assume that the rate of formation of the chain-initiating species is low, so that the maximum concentration of growing polymer chains is built up slowly. This explanation of sigmoid reaction curves was previously suggested by Eley and Pepper (*loc. cit.*) for the polymerisation of *n*-butyl vinyl ether by stannic chloride.

A. G. Evans and Meadows (*J. Polymer Sci.*, 1949, **4**, 359) have shown that in the polymerisation of *iso*butene by boron trifluoride and acetic acid (AcOH) the complex BF_3,AcOH is very much more active than the complex $BF_3(AcOH)_2$, and that the latter may be entirely inactive. We may assume by analogy that in our system we have the equilibria

$$TiCl_4 + 2CCl_3{\cdot}CO_2H \rightleftharpoons TiCl_4{,}2CCl_3{\cdot}CO_2H \quad . \;.\;.\;.\;. \quad (a)$$

$$TiCl_4{,}2CCl_3{\cdot}CO_2H + TiCl_4 \rightleftharpoons 2(TiCl_4{,}CCl_3{\cdot}CO_2H) \quad .\;.\;.\;. \quad (b)$$

where the 1 : 1 complex is the initiating species. It is evident that, when the concentration of the acid is small compared to that of the halide, almost all the acid will be present in the form of the active complex so that the initial rate of chain initiation will be the maximum. If the concentration of acid is increased during the reaction by adding the acid slowly to the reaction mixture, the number of growing chains will increase with time and an acceleration of the reaction will be observed, as was indeed found (Fig. 6).

On the other hand, if the concentration of the catalyst is of the same order as that of the co-catalyst, an appreciable fraction of the latter will be in the form of the inactive complex. The consumption of the active complex by chain initiation will shift the equilibrium, so that more of it is formed and thus the concentration of growing chains increases with time and the reaction curve is sigmoid. Fig. 5 shows how the S-character of the reaction curves becomes more pronounced as the ratio catalyst : co-catalyst is diminished, as is to be expected from this hypothesis.

The S-shaped curves obtained with water vapour as co-catalyst can be explained on the same basis, since the rate of formation of the initiating complex from titanium tetrachloride and an ice dispersion in the circumstances of the experiment can only have been very low. Accordingly, if we conclude that in these experiments the formation of the complex was the rate-governing step, we can now explain the positive temperature coefficient of the over-all reaction rate with water as co-catalyst; for the interaction of a finely divided solid phase (ice) with titanium tetrachloride in solution can be expected to be accelerated by an increase in the temperature so that we may in fact expect a quasi-autocatalytic effect.

It might be thought, by analogy with free-radical polymerisation that the acceleration may be due to the slow consumption of inhibiting impurities. Though this would certainly enhance the effect, it cannot account for it entirely. For if impurities alone were responsible for the effect, a second reaction induced, after partial reaction, in a system in which polymerisation had ceased through consumption of co-catalyst would be expected to show no acceleration. That this is not so is shown by Plesch, Polanyi, and Skinner (*loc. cit.*, Fig. 4), the second reaction showing well-developed acceleration.

The increase in polymerisation rate with decreasing temperature which was found by previous workers (Waterman, *et al.*, *loc. cit.*; Thomas *et al.*, *loc. cit.*; Bresler, *Doklady*, **1945**, **47**, [vi], 410), and in the preliminary experiments in more or less open vessels (Plesch, Polanyi, and Skinner, *loc. cit.*), can be explained tentatively by the supposition that the lower the initial temperature of the reaction mixture, the more atmospheric moisture would condense in the system, and hence that there would be a greater number of particles to participate in the heterogeneous reaction. However, the ill-defined conditions of these experiments make it pointless at present to discuss further the undoubtedly very spectacular explosive polymerisations which take place at very low temperatures.

Norrish and Russell (*loc. cit.*) attempted to explain the acceleration of ionic polymerisations in terms of the inhibition of mutual termination of carbonium and carbanion polymerisation chains by the increasing viscosity of the medium. This theory cannot apply to polymerisations in hydrocarbon media because of the impossibility of separating the ions, even if the possibility of the existence of carbanion polymerisation chains were admitted. In any case, Eley and Pepper (*loc. cit.*) have shown that in the polymerisation of *n*-butyl vinyl ether by stannic chloride in light petroleum the acceleration sets in before there is any marked increase in viscosity. Bresler (*loc. cit.*) also found that ionic polymerisations carried out isothermally could become explosive.

The Chain-transfer Reactions.—Each of the reactions (V) represented in the scheme above is equivalent to a chain-transfer mechanism, because in each case either the catalytic complex or an actual growing chain is reproduced. Eley and Richards (*loc. cit.*) have recently shown that chain transfer can occur in the ionic polymerisation of vinyl ethers. Horrex and Perkins (*Nature*, **1949**, **163**, 486) have shown that chain transfer probably takes place in the low-temperature polymerisation of *iso*butene by boron trifluoride when this is inhibited by olefins, and A. G. Evans and Meadows (*loc. cit.*) have found that in the polymerisation of gaseous *iso*butene by boron trifluoride and acetic acid at room temperature there is a very high degree of chain transfer. The same phenomenon has been found in the course of the present work. Approximately 1×10^{-3} mole of $TiCl_4,CCl_3{\cdot}CO_2H$ complex in contact with gaseous *iso*butene at room temperature produced about 2×10^{-2} mole of polymer of mean molecular weight 400. In the polymerisations carried out at low temperatures the number of moles of polymer produced is usually smaller than the number of moles of co-catalyst. The presence of double bonds in the polymers formed at higher temperatures which was found by Dainton and Sutherland (*J. Polymer Sci.*, **1949**, **4**, 37) and which was confirmed by Flett and Plesch (in the press) for poly*iso*butenes of mean molecular weight up to at least 10^5 can be considered as evidence of chain transfer only if the number of moles of polymer is greater than the number of moles of co-catalyst. In view of the possible occurrence of termination (IV*b*), the mere presence of double bonds is not evidence for chain transfer.

The presence of other olefins during the polymerisation of *iso*butene reduces the molecular weight of the polymer without necessarily affecting the rate (Horrex and Perkins, *loc. cit.*; Thomas *et al.*, *loc. cit.*). Therefore if olefins are produced as products of the normal reaction we could expect a self-poisoning effect by reaction (V*c*). Since according to this scheme the catalytic complex is regenerated there will probably be no effect on the rate but anomalous molecular weights and disappearance of terminal double bonds as the reaction goes to completion might be observable. Double bonds resulting from reaction (V*c*) are probably too inaccessible to take part in any further reaction.

Further work on co-catalysts and inhibitors for this polymerisation is in progress, and the kinetics of isothermal polymerisations are being studied.

I would like to express my gratitude to Professor M. Polanyi, F.R.S., for his help and encouragement in this work, and to my colleagues for many helpful discussions. I thank also Messrs. Imperial Chemical Industries (Billingham) Ltd. for kindly supplying the *iso*butene, the Anglo-Iranian Oil Co. Ltd. for funds which materially assisted the progress of this work, and the Editor of "*Research*" for permission to reproduce Fig. 4.

THE UNIVERSITY, MANCHESTER. [*Received, August* 31*st*, 1949.]

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105. *The Apparent Dipole Moments of the Chlorinated Methanes in the Liquid, Dissolved, and Gaseous States.*

By G. A. BARCLAY and R. J. W. LE FÈVRE.

For CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4, the apparent moments (Debye–Clausius–Mosotti formulæ) in the states given in the title are respectively: 1·19, 1·69, 1·86; 1·14, 1·55, 1·57; 0·97, 1·13, 1·01; and *ca.* 0, 0, 0 (solvent: C_6H_6 in each case). Methylene dichloride thus slightly contravenes those "rules" which relate μ_{gas} to $\mu_{solution}$ *via* the algebraic sign of the Kerr constant of the solute, which for this substance is negative.

Certain empirical equations for the solvent effect are examined and the generality of their applicability tested.

THE substances indicated by the title form a set of readily available related simple structures which are representative of the three chief types of solute molecules encountered in dipole moment measurements, *i.e.*, those with extension respectively (*a*) along the dipole axis (CH_3Cl), (*b*) unequally around it (CH_2Cl_2), (*c*) symmetrically across it ($CHCl_3$), and (*d*) equally about a centre (CCl_4). The original purpose of the present communication was to examine the variations with state of the apparent moments (as indicated by the Debye–Clausius–Mosotti formulæ) of these four compounds *vis à vis* the algebraic signs and magnitudes of their Kerr constants.

Several of the data required for our discussion were already on record in the literature (references below); we have checked or supplemented these where necessary. Dielectric-constant measurements on the system C_6H_6–CH_3Cl do not appear to have been made previously. Table I shows the relevant polarisations at 25° and the moments calculated therefrom, the temperature-invariant term of the Debye equation being used as the true distortion polarisation (${}_{D}P$) in each case.

Table II contains ratios extracted from Table I, together with Sachsse's values for the molar Kerr constants (*Physikal. Z.*, 1935, **36**, 357). It is apparent at once that "rules" requiring the sign of the solvent effect, $\delta\mu$, to be a reversal of that for the electric double refraction, K, are disobeyed by methylene dichloride as a solute, and by this substance and chloroform as undiluted liquids. The comparisons involving *pure* chloroform deserve comment since hitherto this liquid has been regarded as one for which $\delta\mu$ is positive (or $\mu^2_{liq.}/\mu^2_{gas}$ greater than unity; Le Fèvre and Le Fèvre, *J.*, 1935, 1747; Le Fèvre, "Dipole Moments," Methuen, 1938, p. 45; Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374). Such a result was due to the use of the molecular refraction as an approximation for the true distortion polarisation (thus if, in Table I, instead of ${}_{D}P_{CHCl_3} = 25{\cdot}3$ c.c., $[R_L]_D = 21{\cdot}4$ c.c. were used, μ would appear as $1{\cdot}0_7$ D., *i.e.*, 0·06 D. larger than μ_{gas}). With methylene dichloride, however, μ_{gas} exceeds $\mu_{liq.}$ by both methods of calculation ($\mu_{liq.} = 1{\cdot}22$ with $[R_L]_D = 16{\cdot}4$; Vogel, *J.*, 1948, 1849). The "negative" solvent action of benzene on this substance, although slight, resembles in order that reported recently for sulphur dioxide (Le Fèvre and Ross, *J.*, 1950, 283). Thus there are now known two substances, showing definitely negative Kerr constants, for which the $\mu_{C_6H_6}/\mu_{gas}$ ratios are ***less than unity.***

TABLE I.

P in c.c.; μ in D.	CH_3Cl.	CH_2Cl_2.	$CHCl_3$.	CCl_4.	P in c.c.; μ in D.	CH_3Cl.	CH_2Cl_2.	$CHCl_3$.	CCl_4.
$({}_TP)_{gas}$ …	85·3	70·6	46·3	28·1	$({}_OP)_{liq.}$* …	29·1	26·8	19·4	*ca.* 0
${}_DP$ ………	13·6	20·0	25·3	28·1	$({}_OP)_{liq.}$† …	71·7	60·1	31·9	2·3
$({}_OP)_{gas}$ …	71·7	50·6	21·0	*ca.* 0	μ_{gas} ……	$1·8_6$	$1·5_7$	$1·0_1$	*ca.* 0
$({}_TP_\infty)_{C_6H_6}$	72·4	69·4	51·7	28·0	$\mu_{C_6H_6}$ ……	$1·6_9$	$1·5_5$	$1·1_3$	*ca.* 0
$({}_OP_\infty)_{C_6H_6}$	58·8	49·4	26·4	*ca.* 0	$\mu_{liq.}$* ……	$1·1_9$	$1·1_4$	$0·9_7$	*ca.* 0
$({}_TP)_{liq.}$ …	42·7	46·8	44·7	28·0	$\mu_{liq.}$† ……	$1·8_6$	$1·7_0$	$1·2_4$	0·3

* Apparent values by the Clausius–Mosotti–Debye equations.
† Apparent values by the Onsager equation.

TABLE II.

	CH_3Cl.	CH_2Cl_2.	$CHCl_3$.		CH_3Cl.	CH_2Cl_2.	$CHCl_3$.
$\mu^2_{soln.}/\mu^2_{gas}$ ……	0·820	$0·97_6$	1·26	*$\delta\mu_{liq.}/\mu_{gas}$ ……	−0·360	−0·274	−0·040
*$\delta\mu_{soln.}/\mu_{gas}$ ……	−0·0914	$-0·01_3$	+0·119	$K \times 10^{12}$ ……	41	−13·7	−28
$\mu^2_{liq.}/\mu^2_{gas}$ ……	0·406	0·530	0·924				

* $\delta\mu = \mu_{solution}$ or μ_{liquid} minus μ_{gas}.

EXPERIMENTAL.

Data Sources.—Those relating to total polarisations are listed in three groups, by state. In each case the reference providing information for Table I is placed first, others following in chronological order. Although a complete survey of the literature was made, we here omit obviously incorrect or rough determinations.

(*a*) *Gaseous Dielectrics.*—Some authors quote equations for $(\varepsilon - 1)_{T^\circ}$ or $({}_TP_{gas})_{T^\circ}$. Others give individual observations of $(\varepsilon - 1)_{T^\circ}$. The forms used are indicated.

μ, D.	Results as :	Authors.	Reference.
		Methyl chloride.	
1·86	$P = 13·6 + 21{,}351/T$	Smyth and McAlpine	*J. Chem. Physics*, 1934, **2**, 499.
1·97	$\varepsilon - 1 = 0·0_3116 + 2·828/T$	Sänger	*Physikal. Z.*, 1926, **27**, 556.
1·69	Individual $(\varepsilon - 1)_T$	Sircar	*Indian J. Physics*, 1928, **3**, 197.
1·89	One $(\varepsilon - 1)_{100^\circ}$ value	(Calc. by Höjendahl, Thesis, Copenhagen, 1928, from data by Pohrt, *Ann. Physik*, 1913, **42**, 569).	
1·86	$P = 14·72 + 21{,}208/T$	Sänger and Steiger	*Helv. Physica Acta*, 1929, **2**, 130, 411.
1·86	Final μ only	Sänger	*Ibid.*, 1930, **3**, 161.
1·86	Individual $(\varepsilon - 1)_{T^\circ}$	Fuchs	*Z. Physik*, 1930, **63**, 824.
1·86	$P = 14·1 + 21{,}390/T$	Sänger, Steiger and Gächter	*Helv. Physica Acta*, 1932, **5**, 200.
1·92	$P = 8·66 + 22{,}730/T$	Ramaswamy	*Proc. Indian Acad. Sci.*, 1936, *A*, **4**, 108.
		N.B.—Mean of last 8 values = 1·86 D.	
		Methylene dichloride.	
1·58	$P = 19·98 + 15{,}064/T$	Maryott, Hobbs, and Gross	*J. Amer. Chem. Soc.*, 1941, **63**, 659.
1·59	$\varepsilon - 1 = 0·0_21356 + 1·170/T$	Sänger	*Loc. cit.*, 1926.
1·62	Individual $(\varepsilon - 1)_{T^\circ}$	Mahanti and Sengupta	*J. Indian Chem. Soc.*, 1928, **5**, 673.
1·53	$P = 18·74 + 14{,}470/T$	Ramaswamy	*Loc. cit.*
		N.B.—Mean of last 3 values = 1·58 D.	
		Chloroform.	
1·01	$P = 25·28 + 6251/T$	Maryott, Hobbs and Gross	*Loc. cit.*
0·95	$\varepsilon - 1 = 0·0_22127 + 0·4328/T$	Sänger	*Loc. cit.*, 1926.
1·05	Individual $(\varepsilon - 1)_{T^\circ}$	Sircar	*Loc. cit.*
0·99	$P = 24·72 + 6096/T$	Ramaswamy	*Loc. cit.*
1·02	$P = 24·92 + 6491/T$	Ramaswamy	*Loc. cit.*
		N.B.—Mean of last 4 values = 1·00 D.	
		Carbon tetrachloride.	
0	$\varepsilon - 1 = 0·0_22645 + 0·0348/T$	Sänger	*Loc. cit.*, 1926.
0	$P = 28·14 + 0/T$	Ramaswamy	*Loc. cit.*

(*b*) *Solutions in Benzene.*—These are tabulated under self-explanatory headings except that col. 5 shows the moments obtained *via* the true distortion polarisations (cf. Table I), while col. 6 contains those from the figures given by the original authors, who used for ${}_EP + {}_AP$ the refractivities in parentheses.

Substance.	Temp.	No. of solns. examined.	$_\infty P_T$, c.c.	μ, D.	μ, D.	References.
CH_3Cl	25°	6	72·4	1·69	1·72(11·5) *	Present Work.
CH_2Cl_2	25	12	69·4	1·55	1·60(16·4) *	Present Work.
	25	5	70·0	1·56	1·61(15·8)	Mahanti and Das Gupta (*J. Indian Chem. Soc.*, 1929, **6**, 411).
	25	1	66·3	1·50	1·55(16·2)	Müller and Sack (*Physikal. Z.*, 1930, **31**, 815).
	20	1	68·1	1·51	1·59(15)	Müller (*ibid.*, 1933, **34**, 689).
$CHCl_3$	25	15	51·7	1·13	1·21(21·4)	Le Fèvre (*Trans. Faraday Soc.*, 1950, **46**, 1).
	25	4	47·5	1·04	1·10(21·3)	Williams and Krchma (*J. Amer. Chem. Soc.*, 1927, **49**, 1676).
	18	3	55·4	1·19	1·27(21·3)	Hassel and Uhl (*Z. physikal. Chem.*, 1930, *B*, **8**, 187).
	25	1	51·2	1·12	1·18(21·3)	Müller and Sack (*loc. cit.*).
	20	1	51·9	1·12	1·21(21·2)	Müller (*loc. cit.*).
	25	4	52·1	1·14	1·22(21·4)	Le Fèvre and Russell (*J.*, 1936, 491).
CCl_4	25	6	28·0	0	0 (26·5) *	Present Work.
	25	4	28·3	0	0 (28·3)	Williams and Krchma (*loc. cit.*).
	20	1	28·7	0	0 (26·1)	Müller (*Physikal. Z.*, 1933, **34**, 689).

* Values from Vogel (*J.*, 1948, 1842.)

(*c*) *Pure Liquids.*—

Substance.	ε^{25}.	d_4^{25}.	$_TP_{liq.}$, c.c.	Reference.
CH_3Cl	9·68	0·878$_5$	42·7	Extrapolated from values recorded by Ulrich and Nespital (*Z. physikal. Chem.*, 1932, *B*, **16**, 221), Morgan and Lowry (*loc. cit.*), and Goss (*J.*, 1934, 696, 1467).
CH_2Cl_2	8·93	1·3169	46·8	Present work.
	8·92	1·3175	46·7$_5$	Morgan and Lowry (*loc. cit.*).
$CHCl_3$	4·724	1·4790	44·7	Le Fèvre and Rayner (*J.*, 1938, 1921; cf. Ball, *J.*, 1930, 570).
	4·642	—	—	Harris (*J.*, 1925, **127**, 1049).
	4·770	1·4796	45·0	Williams and Krchma (*loc. cit.*).
	4·670	1·4780	44·4	Smyth and Morgan (*loc. cit.*).
	4·899	—	—	Matsuike (*Proc. Imp. Acad. Tokyo*, 1929, **5**, 29).
	4·745	1·4800	44·8	Morgan and Lowry (*loc. cit.*).
	4·722	1·4797	44·7	Jenkins (*J.*, 1934, 480).
	4·709	—	—	Davies (*Phil. Mag.*, 1936, **21**, 1).
CCl_4	2·2270	1·5844	28·18	Le Fèvre (*Trans. Faraday Soc.*, 1938, **34**, 1127).
	2·219	—	—	Harris (*loc. cit.*).
	2·230	1·5835	28·24	Williams and Krchma (*loc. cit.*).
	2·210$_5$	1·584$_2$	27·92	Stranathan (*Physical Rev.*, 1928, **31**, 653).
	2·197	—	—	Matsuike (*loc. cit.*).
	2·231	1·5820	28·27	Morgan and Lowry (*loc. cit.*).
	2·225	1·5836	28·17	Fairbrother (*J.*, 1932, 43).
	2·227$_7$	1·5848	28·19	Jenkins (*loc. cit.*).
	2·226$_6$	—	—	Davies (*loc. cit.*).
	2·2276	1·5846	28·18	Miller (*J. Amer. Chem. Soc.*, 1942, **64**, 117).

Present Measurements.—Methyl chloride (from methyl alcohol, zinc chloride, and hydrochloric acid; Morris and Taylor, *J. Amer. Chem. Soc.*, 1924, **46**, 755), dried by passage through 10% potassium hydroxide solution, concentrated sulphuric acid, and a tower of solid potassium hydroxide, was dissolved in sodium-dried benzene, etc., as described by Le Fèvre and Ross (*loc. cit.*) for sulphur dioxide. The methylene dichloride was a commercial specimen. After standing for several hours over calcium chloride, it was distilled (b. p. 40·1°; d_4^{25} 1·3169) before use. Measurements were made by usual procedures (Le Fèvre, "Dipole Moments," Methuen, 2nd Edn., 1948, pp. 31—42) on apparatus already noted (Le Fèvre and Ross, *loc. cit.*; Calderbank and Le Fèvre, *J.*, 1948, 1949). Extrapolation methods, and symbols used, are explained elsewhere (*Trans. Faraday Soc.*, 1950, **46**, 1) and need not be repeated here.

Methyl chloride in benzene at 25°.

10^6w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.	10^6w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.
0	2·2725	—	0·87378	—	2810	2·4367	5·84	0·87552	0·0619
1370	2·3563	6·12	0·87459	0·0591	2876	2·4384	5·77	0·87560	0·0633
2080	2·3944	5·86	0·87507	0·0620	3418	2·4817	6·12	0·87605	0·0664
2558	2·4246	5·95	0·87540	0·0633					

Whence mean $\alpha\varepsilon_2 = 5\cdot94$; mean $\beta d_2 = 0\cdot0626$; and $_\infty P_1 = 72\cdot4$ c.c.

Methylene chloride in benzene at 25°.

10^5w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.	10^5w_1.	ε^{25}.	$\alpha\varepsilon_2$.	d_4^{25}.	βd_2.
821·8	—	—	0·87599	0·280	6,794	2·4925	3·14	0·89326	0·286
1204	2·3108	3·18	—	—	6,830	2·5117	3·50	0·89365	0·291
1374	2·3120	2·89	0·87769	0·285	8,933	2·5565	3·18	—	—
1722	2·3289	3·27	0·87875	0·289	9,443	2·6027	3·50	0·90128	0·291
2795	2·3602	3·17	0·88217	0·300	12,660	2·6965	3·35	0·91165	0·299
2859	2·3641	3·20	0·88219	0·294	15,010	2·7781	3·37	0·91964	0·306
5088	2·4357	3·21	0·88867	0·293					

Whence (by least squares) $\alpha\varepsilon_2 = 3{\cdot}12 + 2{\cdot}13w_1$; $\beta d_2 = 0{\cdot}286 + 0{\cdot}107w_1$; and ${}_{\infty}P_1 = 69{\cdot}4$ c.c.

The dielectric constant of pure methylene chloride at 25° (*viz.*, 8·93) was read from a graph of condenser reading against ($\varepsilon - 1$), obtained from the following standards: air, $\varepsilon = 1$; C_6H_6, $\varepsilon = 2{\cdot}27$; C_6H_5Cl, $\varepsilon = 5{\cdot}61$; *o*-$C_6H_4Cl_2$, $\varepsilon = 9{\cdot}82$.

*Carbon tetrachloride in benzene at 25°.**

10^6w_1	0	9251	11,034	18,951	20,522	30,908	33,461
ε^{25}	2·2725	2·2724	2·2724	2·2723	2·2723	2·2718	2·2714
d_4^{25}	0·87378	0·87759	0·87810	0·88131	0·88189	0·88609	0·88710

$\Sigma(\varepsilon_{12} - \varepsilon_2)/\Sigma w_1 = -0{\cdot}019$; $\Sigma(d_{12} - d_2)/\Sigma w_1 = 0{\cdot}398$; whence ${}_{\infty}P_1 = 28{\cdot}0$ c.c.

* Recorded at University College, London, 1938—39, with the apparatus of Le Fèvre and Russell (*Trans. Faraday Soc.*, 1947, **43**, 374).

DISCUSSION.

Attempts to relate the variation of the apparent moment of a substance with its state (compare Glasstone, *Ann. Reports*, 1936, **33**, 117, for references not explicitly given here) may be roughly divided into four classes, *viz.*, (*a*) empirical methods of correction for solvent influence, (*b*) *a priori* introduction of factors, for solute and/or for medium, not included in the Clausius–Mosotti–Debye treatment, (*c*) new fundamental models for dielectric polarisation, and (*d*) the addition to the approaches under (*b*) and (*c*) of the conception of hindered rotation, or quasi-crystallinity, in liquids.

Proposals under (*a*) by Müller, Jenkins, Arkel and Snoek, Sugden, Henriquez, *et al.*, like those under (*d*) by Debye (*Physikal. Z.*, 1935, **36**, 100, 193; *Chem. Rev.*, 1936, **19**, 171), Fowler (*Proc. Roy. Soc.*, 1935, *A*, **149**, 1), Kincaid and Eyring (*J. Chem. Physics*, 1938, **6**, 620), and Kirkwood (*J. Chem. Physics*, 1939, **7**, 911; *Ann. N.Y. Acad. Sci.*, 1940, **40**, 315), cannot—in the forms as published—cover those cases (Le Fèvre and Russell, *loc. cit.*; Le Fèvre and Ross, *J.*, 1950, 283; Le Fèvre, Mulley, and Smythe, *J.*, 1950, 290) where $\mu_{\text{soln.}}/\mu_{\text{gas}}$ or $\mu_{\text{liq.}}/\mu_{\text{gas}}$ are greater than unity. Onsager's equation, which falls under (*c*), if used literally, fails with methylene chloride and chloroform (cf. Table I); Wilson's modification (*Chem. Rev.*, 1939, **25**, 377) of it to cover the anisotropy of the solute molecules is an improvement, but one of limited practical usefulness since for most compounds Kerr constant polarisability data are lacking.

In group (*b*) there are the *a priori* treatments of Weigle, Higasi, and Frank, together with others involving the constants ψ and θ of Raman and Krishnan (*Proc. Roy. Soc.*, 1928, *A*, **117**, 589; cf. Goss, *Trans. Faraday Soc.*, 1934, **30**, 751; Le Fèvre and Le Fèvre, *J.*, 1935, 1747; and the criticisms of Jenkins and Bauer, *J. Amer. Chem. Soc.*, 1936, **58**, 2435). In a general way, these approaches have successfully forecast whether $\mu_{\text{soln.}}/\mu_{\text{gas}}$ for a given molecule is above or below unity. In cases where the structure can be credibly regarded as spheroidal, the (*b*) theories have often given approximately quantitatively correct ratios. Unfortunately, in many practical instances, however, neither the ellipsoids defining the anisotropy of polarisability or of "shape" are bodies of rotation. The following table illustrates this point

	(1).			(2).			(3).		
	b_1.	b_2.	b_3.	b_1.	b_2.	b_3.	A.	B.	C.
CH_3Cl	1	0·764	0·764	1	0·827	0·827	1	$0{\cdot}750_5$	0·7505
CH_2Cl_2	—	—	—	1	1·193	0·952	1	1·488	0·878
$CHCl_3$	1	1·349	1·349	1	1·233	1·233	1	1·585	1·585
CCl_4	—	—	—	—	—	—	—	—	—

for the chloromethanes. Under (1) are given the relative polarisabilities recorded for the gaseous materials (Stuart and Volkmann, *Ann. Physik*, 1933, **18**, 140), under (2) the same but for solutions in carbon tetrachloride (Sachsse, *Physikal. Z.*, 1935, **36**, 357), and under (3) the relative effective dimensions (see later) of the molecules. In each case the property measured along the dipole axis is taken as unity.

Several of the relations previously published for solvent action in this field can be cast into general forms typified by: $\mu^2_s/\mu^2_g = 1 + A(\epsilon - 1)/(\epsilon + 2)$. For CH_3Cl, CH_2Cl_2, and $CHCl_3$, the results in Table I require A to be *ca.* −0·60, −0·067, and +0·87, respectively. We find that these figures correspond to $\exp x^2 - (n^2_2)_{\text{Eff.}}/(n^2_1)_{\text{Eff.}}$, where $n^2_{\text{Eff.}}$ is calculated from the distortion polarisation of solvent or solute, *i.e.*, $(n^2_{\text{Eff.}} - 1)M/(n^2_{\text{Eff.}} + 2)d_{\text{liq.}}$, and x^2 is obtained by the following procedure: Scale drawings are constructed from the known X-ray or electron-diffraction data (in the cases just named these are from Sutton and Brockway, *J. Amer. Chem. Soc.*, 1935, **57**, 473; in other instances below, dimensions are those recommended by Pauling and Huggins, *Z. Krist.*, 1934, **87**, 205, and Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1941, **63**, 37) and the "Wirkungsradien" of Stuart (*Z. physikal. Chem.*, 1935, *B*, **27**, 350) superimposed. The maximum measurements along, and in the two perpendicular directions to, the axis of the molecular resultant dipole moment are then read off and recorded as ratios with $A = 1$. Length A is consistently taken parallel to $\mu_{\text{resultant}}$; of B and C (if different), C is made the lesser, x^2 follows as $(C^2 - A^2)/A^2$ when $A > B$ or C, $(C^2 - A^2)/B^2$ when $A < B > C$ and $(C^2 - A^2)/C^2$, when $A < B$ or C. The equation indicated is therefore:

$$\mu^2_{\text{soln.}}/\mu^2_{\text{gas}} = 1 + (\epsilon - 1)[(\exp x^2 - (n^2_2)_{\text{Eff.}}/(n^2_1)_{\text{Eff.}}]/(\epsilon + 2) \quad . \quad . \quad . \quad (1)$$

This is tested in Table III. It is seen that the calculated and observed ratios are in reasonable agreement.

TABLE III.

Substance.	B.	C.	$n^2_{\text{Eff.}}$.	Exp $x^2 - (n^2_2/n^2_1)_{\text{Eff.}}$.	${}_0P_s/{}_0P_g$ (calc.).	${}_0P_s/{}_0P_g$ (found).
CH_3Cl	0·721	0·721	1·929	−0·598	0·82	0·82
CH_2Cl_2	1·488	0·878	2·349	−0·077	0·98	0·98
$CHCl_3$	1·585	1·585	2·368	+0·855	1·26	1·26
$C_6H_5NO_2$	$0{\cdot}752_5$	$0{\cdot}562_5$	2·633	−0·369	0·89	0·87 (1)
C_6H_5Cl	0·767	0·391	2·554	−0·481	0·86	0·84 (2)
C_6H_5Me	$0{\cdot}751_5$	0·485	2·215	−0·573	0·83	0·84 (3)
SO_2	1·453	0·895	1·911	−0·293	0·91	0·99 (4)
Paraldehyde	2·50	2·50	2·499	1·41	1·42	1·69 (5)

References.—Dipole moment values: (1) μ_g = 4·24 (Groves and Sugden, *J.*, 1934, 1094; 1935, 971), μ_{Benzene} = 3·95 (Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). (2) μ_g = 1·73 (Groves and Sugden, *loc. cit.*), μ_{Benzene} = 1·59 (Le Fèvre, *loc. cit.*). (3) μ_g = 0·37 (McAlpine and Smythe, *J. Amer. Chem. Soc.*, 1933, **55**, 453; Baker and Groves, *J.*, 1939, 1144), μ_{Benzene} = 0·34 (Le Fèvre, Le Fèvre, and Russell, *J.*, 1935, 480). (4) μ_g = 1·62 (Le Fèvre, Ross, and Smythe, *J.*, 1950, 276), μ_{Benzene} = 1·61 (Le Fèvre and Ross, *J.*, 1950, 283). (5) μ_g = 1·44 (Le Fèvre, Mulley, and Smythe, *J.*, 1950, 290), μ_{Benzene} = 1·87 (*idem, ibid.*).

Special structures: Chlorinated methanes, Brockway and Sutton, *J. Amer. Chem. Soc.*, 1935, **57**, 473; nitrobenzene, James, King, and Horrocks, *Proc. Roy. Soc.*, 1935, *A*, **153**, 225; paraldehyde, see Le Fèvre, Mulley, and Smythe, *loc. cit.*, for refs.; sulphur dioxide, Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1940, **62**, 1270.

We next explored the possibility of modifying the equation of Le Fèvre and Le Fèvre (*J.*, 1935, 1747) along lines obvious from the discussion of the Raman–Krishnan expression by Govinda-Rao (*Proc. Indian Acad. Sci.*, 1935, **1**, 498), *viz.*, by taking θ as approximately equal to $\mu^2_1 S_1$ and writing S_1 as $4\pi(\delta - 1/3)$, so that

$${}_0P_s/{}_0P_g = 1 + 3\theta(\epsilon - 1)/(\epsilon + 2)4\pi\mu^2 = 1 + 3(\delta - 1/3)(\epsilon - 1)/(\epsilon + 2) \quad . \quad (2)$$

Estimations of δ were made by using the x^2 values as before and applying them in the equations of Maxwell ("Electricity and Magnetism," Vol. 2, Oxford, 1892, Article 438; cf. also Lord Rayleigh, "Scientific Papers," **4**, 307; Mascart and Joubert, "Leçons," 1896, paras. 52, 53, 276) as follows: (when x^2 positive) $\delta = (1/x^2) - \{(1 - x^2)^{\frac{1}{2}} \arcsin x\}/x^3$, or [when x^2 negative, regarding x^2 as $(-1)y^2$] $\delta = [(1 - y^2)/y^2][(1/2y) \ln \{(1 + y)/(1 - y)\} - 1]$. Table IV contains the results for a representative range of molecules; $3\delta - 1$, just as $\exp x^2 - (n^2_2)_{\text{Eff.}}/(n^2_1)_{\text{Eff.}}$ (Table III), correctly forecasts the type of solvent effect; the former quantity, however, does not run parallel to it. Since intuitively it seemed that the appropriate relation might be ${}_0P_s/{}_0P_g$ (or μ^2_s/μ^2_g) $= 1 + f(\epsilon, n^2_{\text{Eff.}})(3\delta - 1)$ many different types of $f(\epsilon, n^2_{\text{Eff.}})$ were tried. Of these, several were promising, *e.g.*,

$${}_0P_s/{}_0P_g = 1 + {}_DP_1(\epsilon_2 + 2)(3\delta - 1)d_2/M_1(\epsilon_2 - 1) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where ${}_{D}P_1$ is the distortion polarisation of the solute and M_1 its molecular weight. Six examples will show, however, that (3) acts in the right sense, but excessively :

	$3\delta - 1$.	${}_{O}P_s/{}_{O}P_g$ (calc.).	${}_{O}P_s/{}_{O}P_g$ (found).		$3\delta - 1$.	${}_{O}P_s/{}_{O}P_g$ (calc.).	${}_{O}P_s/{}_{O}P_g$ (found).
CH_3Cl	−0·274	0·78	0·82	Paraldehyde...	+0·764	1·75	1·69
CH_2Cl_2	−0·055	0·96	0·98	SO_2	−0·238	0·88	0·99
$CHCl_3$	+0·428	1·27	1·26	$C_6H_5{\cdot}NO_2$ ...	−0·409	0·65	0·87

If our " δ " is used in place of the " ξ " of the Ross–Sack equation,

$$\frac{\mu_s}{\mu_g} = \frac{3\varepsilon}{(\varepsilon + 2)} \frac{1 + (n^2_{\text{Eff.}} - 1)\delta}{\varepsilon + (n^2_{\text{Eff.}} - \varepsilon)\delta} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

cited in a previous paper (*J.*, 1950, 283), the ratios indicated are :

	${}_{O}P_s/{}_{O}P_g$ (calc.).		${}_{O}P_s/{}_{O}P_g$ (calc.).
CH_3Cl	0·80	Paraldehyde	1·56
CH_2Cl_2	0·98	SO_2	0·81
$CHCl_3$	1·29	$C_6H_5{\cdot}NO_2$	0·81

Expressions Useful in Practice.—To the above attempts may be urged the objections: (*a*) that the ${}_{D}P$ for a given substance is difficult to measure accurately (examples of this occur in the tables on p. 557; sometimes the A of the Debye equation can be obviously too small without the μ_{gas} value becoming grossly incorrect, *e.g.*, Ramaswamy, *Proc. Indian Acad. Sci.*, 1936, *A*, **4**, 108, gives for acetone $P = 6 + 53650/T$, whence $\mu = 2{\cdot}95$; yet $[R_L]_D$ for this substance is *ca.* 16 c.c.); and (*b*) that knowledge of $n^2_{\text{Eff.}}$ implies the existence of experiments from which μ_{gas} should be calculable directly. Since our underlying motive, for reasons set out elsewhere (" Dipole Moments," Methuen, 1938, p. 52), is to search for an *a priori* method whereby μ_{gas} may be estimated from observations on solutions, we regard (*b*) as serious, and proceed therefore to show the measure of success to be achieved with the accessible quantity $n_D{}^2$, instead of $n^2_{\text{Eff.}}$, in equations (1)—(4).

Table IV summarises our computations for benzene ($n_D{}^2 = 2{\cdot}2417$ at 25°) as solvent. It

TABLE IV.

							μ_{gas}, calc., *via*				
	B.	*C*.	x_2.	δ.	$\mu_{C_6H_6}$.	$n_D{}^2$.	(1).	(2).	(3).†	(4).	$\mu_{\text{gas, obs.}}$
CH_3Cl ...	*	*	−0·520	0·242	1·69	1·7510 (*a*)	1·89	1·76	1·86	1·92	1·86
CH_2Cl_2 ...	*	*	−0·103₅	0·315	1·55	2·0295	1·59	1·56	1·57	1·61	1·57
$CHCl_3$ ...	*	*	+0·602	0·476	1·13	2·0825	1·02	1·06	1·02	1·02	1·01
$CH_3{\cdot}CN$ ...	0·639	0·639	−0·592	0·223	3·11—3·51	1·800	3·49—3·94	3·28—3·70	3·62—4·08	3·58—4·04	3·94—3·98
$CH_3{\cdot}NO_2$	0·865	0·731	−0·466	0·254	3·02—3·13	1·9040	3·30—3·42	3·13—3·56	3·26—3·38	3·35—3·47	3·42
$CO(CH_3)_2$	1·270	0·738	−0·282	0·291	2·74	1·8400	2·95	2·79	2·89	2·96	2·85—3·02
Paraldehyde ...	*	*	+0·840	0·588	1·87	1·989	1·60	1·68	1·50	1·56	1·44
SO_2	*	*	−0·094	0·254	1·61	1·763 (*b*)	1·70	1·67	1·70	1·81	1·62
$N(CH_3)_3$ ...	1·74	1·74	+0·670	0·489	0·86	1·808	0·78	0·80	0·71	0·79	0·64
$C_6H_5{\cdot}CH_3$	*	*	−0·765	0·168	0·34	2·2320	0·37	0·37	0·48	0·40	0·37
C_6H_5Cl ...	*	*	−0·847	0·132	1·59	2·3180	1·74	1·76	2·23	1·93	1·73
$C_6H_5{\cdot}NO_2$	*	*	−0·684	0·197	3·95	2·4045	4·23	4·22	4·79	4·46	4·24
$C_6H_5{\cdot}CN$	0·693	0·353	−0·875	0·117	3·74—3·97	2·329	4·09—4·34	4·10—4·42	5·77—6·13	4·62—4·91	4·39

* See Table III. † Using $[R_L]_D$ instead of ${}_{D}P$. (*a*) Calc. from $[R_L]_D$ *ex* Vogel's (*loc. cit.*) atomic constants. (*b*) *Ex* $[R_L]_D = 9{\cdot}49$ (Nasini, *Gazzetta*, 1883, **18**, 296) and extrapolated density (Le Fèvre and Ross, *loc. cit.*).

Dipole-moment references additional to those beneath Table III : $CH_3{\cdot}CN$: $\mu_{C_6H_6} = 3{\cdot}11$ (Werner, *Z. physikal. Chem.*, 1929, *B*, **4**, 371), 3·51 (Eide and Hassel, *Chem. Ztg.*, 1930, **11**, 2234), 3·16 (Hunter and Partington, *J.*, 1932, 2812), 3·45 (Snoek, *Physikal. Z.*, 1934, **35**, 196), 3·51 (Lewis and Smyth, *J. Chem. Physics*, 1939, **7**, 1085); $\mu_{\text{gas}} = 3{\cdot}98$ (Ramaswamy, *loc. cit.*), 3·94 (Höjendahl, Thesis, 1928), 3·94 (Groves and Sugden, *J.*, 1937, 158). $CH_3{\cdot}NO_2$: $\mu_{C_6H_6}$ (see Faraday Soc. List), $\mu_{\text{gas}} = 3{\cdot}42$ (Smyth and McAlpine, *J. Amer. Chem. Soc.*, 1934, **56**, 1697). Acetone : $\mu_{C_6H_6} = 2{\cdot}74$ (see Faraday Soc. List); $\mu_{\text{gas}} = 2{\cdot}93$ to 3·02 (Stuart, *Z. Physik*, 1928, **51**, 490), 2·85 (Zahn, *Physikal. Z.*, 1932, **33**, 686). Trimethylamine : $\mu_{C_6H_6} = 0{\cdot}86$, $\mu_{\text{gas}} = 0{\cdot}64$ (Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374; cf. Brockway and Jenkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2036). Benzonitrile : ($\mu_{C_6H_6}$ see Faraday Soc. List), $\mu_{\text{gas}} = 4{\cdot}39$ (Groves and Sugden, *loc. cit.*).

will be noted that, by overall consideration, (1) and (2) seem preferable to (3) and (4) for the four aromatic molecules listed. In most cases (1) and (4) could give better results if n_{γ} were used instead of n_D, since n_{γ} is nearer to $n_{E\infty}$ than is n_D.

Variation of $\mu_{\text{Nitrobenzene}}$ *with Solvent.*—An empirical " rule," if of correct form, should also forecast the relative effects of different solvents upon a given solute. Table V shows the application of equations (1), (2), and (4), using n_D^2 instead of $n^2_{E\infty}$, to the figures conveniently tabulated for nitrobenzene in 12 solvents by Cleverdon and Smith (*Trans. Faraday Soc.*, 1949, **45**, 109) ($\mu_{\text{gas}} = 4{\cdot}24$).

TABLE V.

			${}_0P_s/{}_0P_g$, calc., *via* eqn.:			
Solvent.	ϵ_{25}.	$(n_D^2)_{25}$.	1.	2.	4.	${}_0P_s/{}_0P_g$, found.
n-Hexane	1·887	1·8847	0·94	0·91	0·87	0·91
Di*iso*amyl	1·976	1·9773	0·92	0·90	0·85	0·88
*cyclo*Hexane	2·016	2·0221	0·91	0·90	0·84	0·88
Decalin	2·162	2·16	0·89	0·89	0·81	0·86
Dioxan	2·204	2·0171	0·91	0·89	0·80	0·85
CCl_4	2·228	2·1656	0·89	0·88	0·80	0·86
p-Xylene	2·260	2·2317	0·87	0·88	0·79	0·85
C_6H_6	2·273	2·2417	0·87	0·88	0·79	0·87
CS_2	2·633	2·6360	0·79	0·86	0·71	0·75
Et_2O	4·250	1·8295	0·87	0·79	0·45	0·57
$CHCl_3$	4·722	2·0825	0·80	0·77	0·40	0·55
C_6H_5Cl	5·612	2·3180	0·72	0·75	0·32	0·34

For the nine non-polar solvents, all three relations predict drifts in the direction observed, and for this class (1) seems on the whole superior to (4). The latter, however, alone reflects the effects of the three polar media. Further, it should be repeated again that $n^2_{E\infty}$ properly enters (4), *not* n_D^2, which has been utilised only because for most substances it is a recorded (or easily determinable) datum.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, November 5th, 1949.*]

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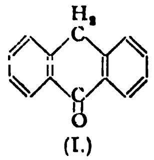
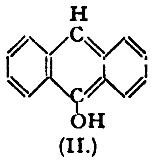
106. *The Polarities of Enols.*

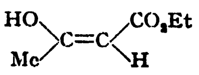
By C. L. ANGYAL and R. J. W. LE FÈVRE.

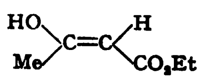
The following dipole moments are recorded (refractivity method; solvent, benzene): anthrone, 3·5 D., ethyl salicylate, 2·7 D., ethyl *p*-hydroxybenzoate, 2·8 D. The moment of anthranol has been estimated as 1·9—2·0 D., *i.e.*, greater than is usual for phenols and naphthols.

THE experiments now recorded were part of an attempt to examine the polarities of enols. The literature reveals that compounds possessing the ·C(OH):CH·CO· unit in a manner such that internal chelation is unlikely for stereo-structural reasons (*e.g.*, dimedone; Hukins and Le Fèvre, *J.*, 1949, 898) are unusually acidic (Taylor and Ewbank, *J.*, 1926, 2818; Bennett, *Chem. and Ind.*, 1926, 960). Phenols, naphthols, etc., also have this quality and can of course be regarded as enols containing the simpler fragment ·C(OH):CH·, yet in no such case has the dipole moment of the corresponding keto-isomeride been recorded. Anthrone (I) and anthranol (II) initially seemed to be a pair of molecules with the desired relationship, since, in solution, they form ultimately an equilibrium with (I) predominating (Beilstein, " Handbuch, etc.," VII, 473; VII*, 257; Meyer, *Annalen*, 1911, **379**, 37; 1913, **396**, 133; 1920, **420**, 113). It later transpired that 100% pure anthranol has never been isolated (Bäckstrom and Beatty, *J. Physical Chem.*, 1931, **35**, 2531). We therefore proceeded first to study anthrone itself in benzene, to obtain its specific polarisations at given concentrations (cf. Table I), and then to prepare a succession of separate


(I.)


(II.)


(III.)


(IV.)

quantities of "anthranol," each being analysed by the iodine procedure of Bäckstrom and Beatty (*loc. cit.*) and, simultaneously, submitted to dielectric-polarisation measurements as though it were a single substance. Anthranol contents ranging from 18 to 45% were obtained. On the assumption that only (I) and (II) are concerned, and that a simple mixture rule applies to the observed specific polarisations, moments up to 2 D. were indicated for (II). Reproducibility was, however, poor and continued to be so despite all efforts at improvement.

An estimate of similar order follows from the moment now found for anthranol methyl ether (1·5 D.). Noting that between a phenol and its methyl ether there is commonly a polarity difference of 0·4—0·5 D., it would seem that anthranol has a moment of 1·9—2·0 D., *i.e.*, some 1·5 D. lower than that of anthrone, but notably higher than those of phenol (1·6—1·7) or the two naphthols (1·0—1·5). Attempts to prepare equilibrium mixtures from the ketonic isomeride in benzene or hexane have also been made, but unsuccessfully—a not unexpected result since Meyer's experiments (*Annalen*, 1913, **396**, 133) suggest that strong electrolytes are required. Further, it is relevant that infra-red spectroscopic methods have not shown the presence of any enol form of anthrone in carbon tetrachloride solutions (Flett, *J.*, 1948, 1441).

We have also prepared 9-phenanthrol, but found it to be too sparingly soluble in benzene for measurement.

Dipole Moments of Ethyl Salicylate and p-*Hydroxybenzoate.*—Results for these two compounds are given below. Le Fèvre and Welsh (*J.*, 1949, 1909) estimated the moment of the enolic form of ethyl acetoacetate as 1·7 D. Since this enol might exist as a *cis*- or a *trans*-form, (III) or (IV), it seemed of interest to examine ethyl salicylate and ethyl *p*-hydroxybenzoate—molecules in which the hydroxyl groups and carbethoxy-groups are in the same relative configurations as in (III) and (IV). However, the moments observed (2·7 and 2·8 D., respectively) are too nearly equal to be relevantly useful. It is notable that the parent *o*- and *p*-acids also have similar moments (2·63 and 2·73 D.; Wilson and Wenzke, *J. Amer. Chem. Soc.*, 1935, **57**, 1265).

EXPERIMENTAL.

Materials.—Anthrone was prepared from anthraquinone (*Org. Synth.*, Coll. Vol. I, p. 60) and recrystallised from a benzene–light petroleum (3 : 1); m. p. 152°. Anthranol-containing specimens were obtained and analysed as described by Bäckstrom and Beatty (*loc. cit.*).

Anthranol methyl ether was isolated directly from anthrone by the method of Meyer and Schlösser (*Annalen*, 1920, **420**, 126) and crystallised from a little light petroleum; m. p. 93·5—94·5°.

The ethyl salicylate was a fractionated commercial specimen, b. p. 230—232°. Its *p*-isomer was from a similar source, and was recrystallised from water to m. p. 116°.

Measurements.—These were made by routine methods (cf. *J.*, 1948, 1949) and are tabulated below under the usual headings. The solvent used was benzene throughout.

Anthrone.

$10^5 w_1$	238	373	604	878	972	1177	1489	1657
ε^{25}	2·289	2·299	2·317	$2{\cdot}338_8$	2·346	2·366	2·389	2·401
d_4^{25}	0·87434	0·87474	0·87528	0·87556	0·87620	0·87676	0·87710	0·87690
P_1 (c.c.) ...	298	302	312	321	317	329	326	326

Whence $\alpha\varepsilon_2 = 7{\cdot}02 + 56w_1$; $\beta d_2 = 0{\cdot}259_5 - 2{\cdot}9w_1$.

Anthranol methyl ether.

$10^5 w_1$	1277	1836	2451	2928	3660	4064
ε^{25}	2·2907	2·2960	2·3074	2·3111	2·3226	2·3283
d_4^{25}	0·87650	0·87808	0·87940	0·88056	0·88336	0·88419

Whence $\alpha\varepsilon_2 = 1{\cdot}36_5$ (mean); $\beta d_2 = 0{\cdot}238$ (mean).

Ethyl salicylate.

$10^6 w_1$	9215	12,060	17,932
ε^{25}	2·3164	2·3301	2·3605
d_4^{25}	0·87620	0·87536	0·87676

Whence $\alpha\varepsilon_2 = 4{\cdot}82$ (mean); $\beta d_2 = 0{\cdot}187$ (mean).

Ethyl p-*hydroxybenzoate.*

$10^6 w_1$	2908	3977	4483	5589	5656	6414
ε^{25}	2·2872	2·2942	2·2975	2·3020	2·3028	2·3053
d_4^{25}	0·87468	—	0·87486	—	0·87520	—

Whence $\alpha\varepsilon_2 = 5{\cdot}31$ (mean); $\beta d_2 = 0{\cdot}267$ (mean).

Results.—These have been calculated *via* the equations $\infty P_T = M_1[p_2(1 - \beta) + C\alpha\varepsilon_1]$, and $\mu = 0{\cdot}221(\infty P_T - R_L)^{\frac{1}{2}}$ (at 25°; cf. Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). For benzene, $p_2 = 0{\cdot}3409$ c.c. and $C = 0{\cdot}1881$.

Substance.	M_1.	$(\alpha\varepsilon_2)_{w_1=0}$.	$(\beta)_{w_1=0}$.	∞P_T.	$[R_L]_D$.	μ, D.
Anthrone	194·1	7·02	0·297	302·8	57·5 *	3·46
Anthranol methyl ether	208·1	$1{\cdot}36_5$	0·272	105·1	61·5 *	1·46
Ethyl salicylate	166·1	4·82	0·214	195·1	44·8 †	2·71
Ethyl *p*-hydroxybenzoate ...	166·1	5·31	0·306	205·2	43·3 *	2·81
					44·1 ‡	2·80

* Calc. from atomic and bond refractions. † Cf. I.C.T., vol. I, 227.

‡ Calc. from ethyl benzoate (42·6 c.c.) and hydroxylic oxygen (1·5 c c.).

Previous Determinations.—These are as follows: Anthrone: $(\infty P_T)_{20^\circ} = 341$ c.c. in benzene, and $\mu = 3{\cdot}66$ D. using $[R_L]_D = 58$ c.c. (Coomber and Partington, *J.*, 1938, 1444). Ethyl salicylate: $\mu = 2{\cdot}88$ D. in benzene at 40·2° (Hrynakowsky and Kalinowsky, *Compt. rend.*, 1933, **197**, 483; actual polarisations not recorded).

Our results for anthrone differ from those of Coomber and Partington in that their P_1 values, calculated by the usual mixture relation, *increased* with dilution, while ours *decrease*. Consequently, our final μ (3·46) is lower than theirs (3·66). We therefore mention that the above eight anthrone solutions have been examined singly or in pairs on occasions widely spaced over nine months, and have involved different batches of benzene. The contrast cannot easily be ascribed to instrumental "drifts," evaporation, etc.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, November 7th*, 1949.]

107. *The Significance of the Bromine Cation in Aromatic Substitution. Part I. Kinetic Evidence.*

By D. H. DERBYSHIRE and WILLIAM A. WATERS.

Hypobromous acid in mineral acid solutions becomes a powerful brominating agent on account of the production of bromine cations: $H^+ + HOBr \rightleftharpoons (H_2OBr)^+$.

This has been established by brominating sodium toluene-ω-sulphonate with hypobromous acid in the presence of perchloric acid as catalyst and demonstrating that $k_{\text{bi.}}/[H^+]$ is very nearly constant. This reaction exhibits a slight negative "primary salt effect," as would be anticipated on the Brønsted–Bjerrum theory of reaction rates.

Bromination of benzoic acid is a similar reaction, but at high concentrations of the acid catalysts (sulphuric and perchloric acid) the bimolecular reaction velocity rises abnormally. This concentration effect can, in the main, be related to the magnitude of Hammett's "acidity function," H_0, but in addition a positive linear "salt effect" can be discerned.

At pH 7—8 the relative brominating powers of molecular hypobromous acid and molecular bromine have been compared, by use of sodium *p*-anisate as the reactant. Molecular bromine appears to be about 2000 times as active an agent as hypobromous acid, but buffer salts evidently react with the latter to produce other complex brominating agents, such as $(Br{\cdot}HPO_4)^-$. The ion $(Br_3)^-$ does not seem to have any detectable brominating power.

MOST investigators of bromine substitution seem to concur with the view (Ingold, Smith, and Vass, *J.*, 1927, 1245; Ingold, *Chem. Reviews*, 1934, **15**, 271) that the polar reactivity of a reagent Br—X depends upon its polarisability to the activated state, $\overset{\delta+}{Br}\!\!-\!\!\overset{\delta-}{X}$, and can be related to the electron affinity of X, thus:

most reactive Br—Cl > Br—Br > Br—OH *least reactive*

Experimental evidence for this view was put forward by Francis (*J. Amer. Chem. Soc.*, 1925, **47**, 2341) who found that at about pH 3 bromine water reacted with *m*-nitrophenol at about a thousand times the speed of free hypobromous acid, and developed the view that the true brominating agent might in each case be the bromine cation, Br^+. Later, however, his conclusions were criticised severely by Alexander (*J.*, 1938, 729) who studied the bromination of phenols on the surface of M/100-sulphuric acid and decided that hypobromous acid was a powerful brominating agent. Much earlier, Stark (*Ber.*, 1910, **43**, 671) reported that hypobromous acid, prepared by shaking a 10% suspension of bromine in water with mercuric oxide and filtering the resulting solution, readily brominated both benzene and toluene, and even converted benzoic into *m*-bromobenzoic acid in 89% yield in 24 hours, whereas bromine water had not this reactivity.

Whilst a number of workers (*e.g.*, Baines, *J.*, 1922, **121**, 2810; Bartlett and Tarbell, *J. Amer. Chem. Soc.*, 1936, **58**, 467) have studied the effects of acids and of bromide anions on the equilibrium $Br_2 + H_2O \rightleftharpoons HOBr + H^+ + Br^-$ and their implications for addition and substitution reactions in which polarised molecules, such as $\overset{\delta+}{\mathrm{Br}}\text{—}\overset{\delta-}{\mathrm{Br}}$ rather than free bromine cations, Br^+, may be involved, very few appear to have examined the effects of acids on bromide-free solutions of hypobromous acid. As already reported in brief (*Nature*, 1949, **164**, 446) we were surprised to find that, though free hypobromous acid has no tendency to react with benzene in dilute aqueous solution, yet on the addition of a mineral acid bromination readily occurs. Evidently the discrepancy between the results of Francis and of Alexander is due to the different acidities of their media; the results of Stark, which we have ourselves confirmed, are also explicable by the fact that his reagent is noticeably acidic; it had pH 2—3 when examined with a pH meter using a glass electrode.

As we have stated (*loc. cit.*), this enhanced reactivity of hypobromous acid in acidic media can be explained by the hypothesis that a rapid reversible reaction with hydrogen ions occurs to give either free bromine cations

$$H^+ + HOBr \rightleftharpoons H_2O + Br^+ \quad . \; . \; . \; . \; . \; . \; . \; . \quad (1a)$$

or the complex hydrated bromine cation $(H_2OBr)^+$ which is the conjugate acid of the very weak base HOBr :

$$H^+ + HOBr \rightleftharpoons (H_2OBr)^+ \quad . \; . \; . \; . \; . \; . \; . \; . \quad (1b)$$

According to this view, hypobromous acid can behave as a brominating agent in the same way as nitric acid behaves as a nitrating agent (Gillespie and Millen, *Quart. Reviews*, 1948, **2**, 277), though since the intensely reactive bromine cation can be formed at much lower acidities than can the NO_2^+ cation it may perhaps react as the solvated entity $(H_2OBr)^+$, comparable with the nitracidium ion $(H_2NO_3)^+$ (cf. Halberstadt, Hughes, and Ingold, *Nature*, 1946, **158**, 514).

Though at first we thought that our experimental findings were novel, we have now seen that exactly the same theory had already been advanced by Shilov and Kaniaev in 1939 [*Compt. rend.* (*Doklady*) *Acad. Sci. U.R.S.S.*, 1939, **24**, 890] who studied the bromination of the sodium salt of anisole-*m*-sulphonic acid by bromine-free hypobromous acid and showed that it was a second-order reaction which proceeded at a rate which was nearly proportional to the hydrogen-ion concentration of the medium. We now report the results of similar studies of two other aromatic substrates, (*a*) sodium toluene-ω-sulphonate and (*b*) benzoic acid, which we selected because they are not attacked by bromine-water.

In M/200-aqueous solution at 21·5°, sodium toluene-ω-sulphonate does not react with vacuum-distilled, bromide-free hypobromous acid; a mixture at pH 5·18 (glass electrode) showed no drop in titre during 30 minutes. Similar mixtures brought to pH 2 by the addition of perchloric acid had half-reaction periods of about 15 minutes, and the usual tests of varying [HOBr] and $[Ph{\cdot}CH_2{\cdot}SO_3Na]$ independently showed that the substitution was a process of first order with respect to each of these reactants and strictly second order as a whole, until the substitution was more than 90% complete.

TABLE I.

Bromination of sodium toluene-ω-sulphonate with hypobromous acid at 21·5° in the presence of perchloric acid.

HOBr, M., $\times 10^{-3}$.	$Ph{\cdot}CH_2{\cdot}SO_3Na$, M., $\times 10^{-3}$.	$HClO_4$, M., $\times 10^{-2}$.	k (bimolec.), observed (mole/l./sec.).	$k_{cat.}$ ($= k_{bi.}/HClO_4$).	Total ionic strength, M.
4·73	7·09	9·41	1·28 ± 0·03	$13{\cdot}5_4$	0·1013
3·47	14·18	4·71	0·66 ± 0·03	$14{\cdot}0_1$	0·0613
4·38	7·09	4·71	0·675 ± 0·02	$14{\cdot}3_4$	0·0542
3·91	7·09	2·36	0·345 ± 0·01	$14{\cdot}7_4$	0·0306
4·08	7·09	0·942	0·146 ± 0·002	$15{\cdot}4_8$	0·0165
3·99	7·09	0·471	0·0723 ± 0·0006	$15{\cdot}3_5$	0·0118
4·61	7·09	$2{\cdot}36 \times 10^{-2}$ $HClO_4$ plus $7{\cdot}06 \times 10^{-2}$ $NaClO_4$	0·313 ± 0·005	$13{\cdot}2_9$	0·1013
3·39	7·09	$2{\cdot}36 \times 10^{-2}$ $HClO_4$ plus $2{\cdot}36 \times 10^{-2}$ LiCl	falls with time from 0·23 to 0·17		

From Table I, which summarises our results, it will be seen that $k_{cat.}$ falls by only 12% for a 20-fold change in the perchloric acid concentration, and that it drops steadily as the total ionic strength of the solution is increased. At the dilutions which we have used, both perchloric acid and sodium toluene-ω-sulphonate will be ionised completely. Hence it is the toluene-ω-sulphonate anion which is really substituted and consequently the slight variation of $k_{cat.}$ with dilution is ascribable to a "primary salt effect" (cf. R. P. Bell, "Acid-Base Catalysis," Chap. 2, Oxford, 1941) as the following analysis will show.

Using the Brønsted–Bjerrum theory of reaction rates in solution we may write the equilibrium (1, *b*) above as

$$K = \frac{[H_2OBr^+]}{[H^+]\,.\,[HOBr]} \times \left\{\frac{f_{H_2OBr}}{f_{H^+}\,.\,f_{HOBr}}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

and the substitution reaction as

$$(H_2OBr)^+ + (Ph{\cdot}CH_2{\cdot}SO_3)^- \xrightarrow{k_2} H_2O + H^+ + (C_6H_4Br{\cdot}CH_2{\cdot}SO_3)^- \quad . \quad . \quad (2)$$

Velocity of reaction, $v = k_2[H_2OBr^+][Ar^-] \times \left\{\frac{f_{H_2OBr^+}\,.\,f_{Ar^-}}{f_{tr.}}\right\}$

where Ar^- is the aromatic anion which is brominated and $f_{tr.}$ is the activity coefficient of the transition complex of the bromination reaction.

Hence $$v = Kk_2[H^+][HOBr][Ar^-] \times \left\{\frac{f_{Ar^-}\,.\,f_{H^+}\,.\,f_{HOBr}}{f_{tr.}}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

Writing $k_{bimolec.}$ (measured) $\times$ $[HOBr]\,.\,[Ar^-] = k_{cat.}[H^+][HOBr][Ar^-]$

we have $$k_{cat.} = Kk_2\left\{\frac{f_{Ar^-}\,.\,f_{H^+}\,.\,f_{HOBr}}{f_{tr.}}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (C)$$

At ionic strengths, μ, of under 0·1 mol./litre, the Debye–Hückel expression, $-\log_{10} f_i = Az_i^2\mu^{\frac{1}{2}}$, may be applied for each ion involved, z_i being the charge on each reactant concerned, and hence equation (C) above gives

$$\log_{10} k_{cat.} = \log k_0 - A\mu^{\frac{1}{2}}(z^2_{Ar^-} + z^2_{H^+} - z^2_{tr.}) = \log k_0 - \mu^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad (D)$$

where $\log k_0 = \log_{10} Kk_2$ at infinite dilutions, and μ is the total ionic strength of the solution, since our reaction is one between univalent ions of opposite electrical charge and the theoretical values for A and $z_{tr.}$ are 0·5 and zero respectively. Thus in theory we should expect that the reaction would exhibit a *negative* primary-salt effect, and that the graph of $\log_{10} k_{cat.}$ against $\mu^{\frac{1}{2}}$ should have a limiting gradient of −1 in extremely dilute solution.

Fig. 1 shows that our experimental data accord with an equation of the form (D) though the slope of our plot (found, 0·3) is somewhat lower than the theoretical value. In particular we would draw attention to the fact that point X on the graph, corresponding to the experiment in which 0·0706N-sodium perchlorate was added to a 0·0236N-perchloric acid solution so as to bring μ up to the value for the strongest acid catalyst used, falls satisfactorily on the linear plot.

The low gradient of our graph is a natural consequence of the use of solutions somewhat more concentrated than those to which the Debye–Hückel theory is properly applicable, and the deviation may possibly be related to the fact that the transition complex of the attack of the bromine cation on the aromatic nucleus of the toluene-ω-sulphonate anion is not a simple electrically neutral entity but a large dipole, since the bromine cation approaches an uncharged carbon centre remote from the sulphonate group.

It may be noted that a similar negative salt effect seems to influence the substitution studied by Shilov and Kaniaev, in which again the reactants are ions of opposite charge, *viz.*, $(MeO{\cdot}C_6H_4{\cdot}SO_3)^-$ and $(H_2OBr)^+$.

Whilst the addition of sodium perchlorate to a reaction mixture had only a small effect on the reaction velocity, the addition of a smaller concentration of lithium chloride has a much greater effect. It noticeably decreased the rate of bromination and complicated the reaction kinetics. This may be ascribed to the setting up of the further equilibrium (3). It would appear that bromine chloride is a less active brominating agent than the bromine cation

$$(H_2OBr)^+ + Cl^- \rightleftharpoons Br{-}Cl + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(cf. Shilov and Kaniaev, *loc. cit.*). Since similar equilibria (4), giving other electrically neutral brominating agents of uncertain reactivities, would be set up by adding salts of weak acids to

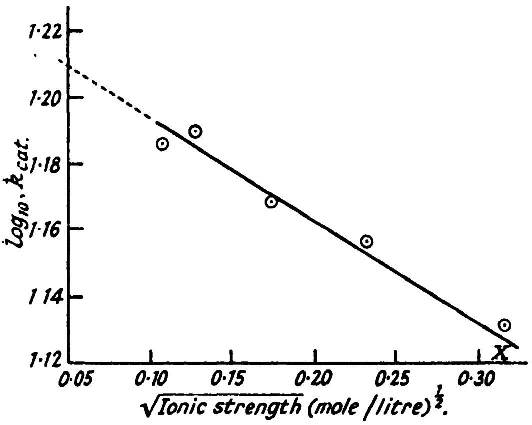
$$(CH_3{\cdot}CO_2)^- + (H_2OBr)^+ \rightleftharpoons CH_3{\cdot}CO_2{-}Br + H_2O \quad . \quad . \quad . \quad . \quad . \quad (4)$$

our reaction mixtures (cf. Mauger and Soper, *J.*, 1946, 71) it is not possible to extend the range of these studies of the reactivity of the bromine cation by carrying out reaction velocity measurements in buffered solutions in the range pH 3—6.

Somewhat different results have been obtained from our study of the bromination of benzoic acid. For this, in order to obtain an adequate concentration of the reactant, we had to use 40% acetic acid as the solvent, and as catalysts we took both perchloric and sulphuric acids over the concentration range 0·1—2·5N. Consequently the aromatic substrate was always the undissociated benzoic acid molecule. Tests showed that even in our most concentrated mineral acid catalysts the acetic acid was not attacked by the bromine cation, and a larger-scale preparation confirmed that *m*-bromobenzoic acid was the main reaction product.

FIG. 1.

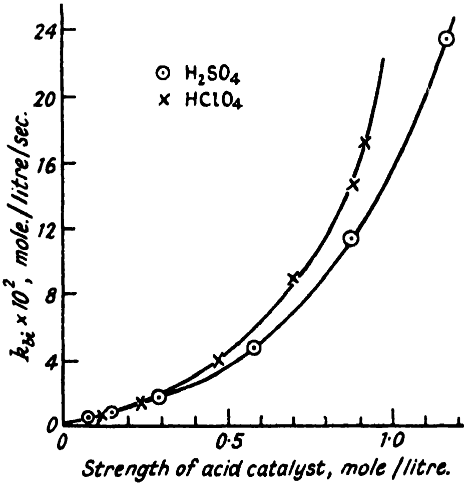
Bromination of sodium toluene-ω-sulphonate with hypobromous acid.



Relationship between log $k_{cat.}$ *and* $\sqrt{ionic\ strength}$.

FIG. 2.

Bromination of benzoic acid with bromine cation.



Relationship between $k_{bi.}$ *and acid concentration.*

Fig. 2 shows that both perchloric and sulphuric acid catalyse the reaction between hypobromous and benzoic acids to an extent which is roughly proportional to the mineral acid concentration up to 0·3N., but that at high acid concentrations the value of $k_{cat.}$ increases as [Acid] increases, and sulphuric acid then becomes somewhat less effective as a catalyst than perchloric acid.

Though the Debye–Hückel theory is unable to predict the nature of the salt effects which influence reactions between ions and neutral molecules, an enhanced catalytic effect at high acid concentrations can be expected from analogy with hydrogen-ion-catalysed reactions, such as sucrose hydrolysis, in strong mineral acid solutions. For such reactions Hammett (*Chem. Reviews*, 1935, **16**, 67; "Physical Organic Chemistry," Chap. 9, New York, 1940; Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 830) from studies of indicators of the type $I + H^+ \rightleftharpoons HI^+$ has defined expressions (E) for experimentally measurable "acidity

$$H_0 = pK_a - \log_{10}\frac{[HI^+]}{[I]} = -\log_{10}\left\{a_{H^+}\frac{f_I}{f_{HI^+}}\right\}; \text{ and } h_0 = a_{H^+}\frac{f_I}{f_{HI^+}} \quad . \quad . \quad . \quad (E)$$

functions" H_0, h_0, which were found to be independent of the nature of the indicator chosen. He therefore suggested that in strong acid solutions h_0 might be used to replace the activity coefficient factors in the usual Brønsted–Bjerrum salt-effect equations. Indeed he showed experimentally that the kinetic expressions (F)

$$k = \text{Const.} \times h_0 \text{ and } \log_{10} k = -H_0 + \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (F)$$

could often replace the ideal equation $k = \text{Const.} \times [\text{H}^+]$ which holds satisfactorily for very dilute solutions only.

Fig. 3, in which Hammett's acidity function H_0 for aqueous sulphuric acid (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827) has been plotted against $\log_{10} k_{\text{observed}}$ for the sulphuric-acid-catalysed bromination, shows that his velocity relationship (F) holds at low acidities, when $k_{\text{cat.}}$ is approximately constant, but that at higher acidities k_{observed} increases rather more rapidly, since $\log_{10} k_{\text{observed}}$ becomes a linear function of H_0 with a gradient of $-1{\cdot}7$ instead of the expected value of $-1{\cdot}0$. It is improbable that this discrepancy can be due to the use of 40% acetic acid as the solvent, since Paul and Hammett (*ibid.*, 1936, **58**, 2182) have reported that H_0 for sulphuric acid is almost the same in 50% acetic acid as in water. A similar positive deviation of substitution rates from acidity functions has been noted for aromatic nitrations in 80—90% sulphuric acid (Gillespie and Millen, *loc. cit.*).

Now for the bromination of undissociated benzoic acid we may write (G):

$$k_{\text{obs.}}[\text{Benz}][\text{HOBr}] = Kk_2[\text{HOBr}][\text{H}^+][\text{Benz}]\left\{\frac{f_{\text{HOBr}}\cdot f_{\text{H}^+}\cdot f_{\text{Benz}}}{f_{tr^+}}\right\} \quad . \quad . \quad \text{(G)}$$

and hence

$$k_{\text{observed}} = Kk_2[\text{H}^+]\left\{\frac{f_{\text{H}^+}\cdot f_{\text{HOBr}}}{f_{\text{H}_2\text{OBr}^+}}\right\} \times \left\{\frac{f_{\text{H}_2\text{OBr}^+}\cdot f_{\text{Benz.}}}{f_{tr^+}}\right\} \quad . \quad . \quad . \quad . \quad \text{(H)}$$

If Hammett's acidity function hypothesis is to be followed, then we should compare the activity factor $\left\{\frac{f_{\text{H}^+}\cdot f_{\text{HOBr}}}{f_{\text{H}_2\text{OBr}^+}}\right\}$ with the expression $\left\{\frac{f_{\text{H}^+}\cdot f_{\text{I}}}{f_{\text{HI}^+}}\right\}$ for an indicator system, since equilibrium (1*b*) is exactly that corresponding to a weakly basic indicator. Equation (H) above, however, shows clearly that the bromination which we have studied depends also on the ensuing chemical reaction between the $(\text{H}_2\text{OBr})^+$ cation and the benzoic acid molecule, and for this reaction the further activity factor product $\left\{\frac{f_{\text{H}_2\text{OBr}^+}\cdot f_{\text{Benz.}}}{f_{tr^+}}\right\}$ must be taken into account. Since high concentrations of ions and molecules are involved it would be expected that our reaction should exhibit a positive *linear* salt effect (cf. R. P. Bell, *op. cit.*; Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," p. 62, New York, 1941) ascribable to the net value of the activity-coefficient expression given immediately above. The extended Debye–Hückel theory would then lead to the expression (I)

$$\log_{10} k_{\text{observed}} = -H_0 + B\mu + \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(I)}$$

and since at high acid concentrations H_0 becomes nearly a linear function of the mineral acid concentration (Hammett and colleagues, *loc. cit.*) the "salt effect" represented by the term $B\mu$ in equation (I) may be written as bH_0. Equation (I) then reduces to (J)

$$\log_{10} k_{\text{observed}} = -(1 + b)H_0 + \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(J)}$$

and in this way the shape of the graphical results of Fig. 3 becomes explicable. This theoretical approach is however far too approximate for any attempt at quantitative treatment.

Table II shows that neutral salts still further increase the rate of bromination of benzoic acid in both sulphuric and perchloric acid. This may be due both to the positive salt effect discussed above and to the effect of neutral salts on the acidity function H_0 (Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 828).

TABLE II.

The effect of neutral salts on the bromination of benzoic acid by bromine cations at 21·5°.

Acid.	Salt added.	$k_{\text{bi.}}$ (found).
H_2SO_4 0·294M.	—	0·01626 mol./l./sec.
H_2SO_4 0·294M.	NaNO_3 1·3M.	0·0689 ,,
HClO_4 0·448M.	—	0·036 ,,
HClO_4 0·448M.	NaClO_4 0·448M.	0·0547 ,,
HClO_4 0·224M.	—	0·012 ,,
HClO_4 0·224M.	NaClO_4 0·672M.	0·0242 ,,

In the concentration range which we have used, the acidity functions for sulphuric and perchloric acids are almost identical. The slight deviation in the catalytic reactivities of these two acids may perhaps be due to the intervention of the equilibrium (5)

$$(\text{H}_2\text{OBr})^+ + (\text{SO}_4)^{--} \rightleftharpoons (\text{SO}_4\text{Br})^- + \text{H}_2\text{O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

since the second dissociation constant of sulphuric acid is low enough for the $(SO_4)^{--}$ anion to function as a base. From the relevant equations for the equilibria concerned, it is easily possible to derive the expression (K)

$$[SO_4Br^-] = \text{Const.}\ [HOBr][HSO_4^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (K)$$

which is similar to those used by Mauger and Soper (*loc. cit.*) in considering the effects of buffers on certain substitution reactions of hypochlorous acid. From equation (K) it can be seen that there should be an increasing conversion of highly active $(H_2OBr)^+$ cations into inactive $(SO_4Br)^-$ as the concentration of the sulphuric acid is increased, though this should not be an effect of the same order as the increasing conversion of neutral HOBr into $(H_2OBr)^+$.

The Relative Reactivities of Hypobromous Acid and Molecular Bromine.—The foregoing work has shown that the relative rates of bromination by means of molecular hypobromous acid and molecular bromine cannot be compared in appreciably acid solution. To confirm the correctness of the polarity theory of Ingold, we have made a direct comparison of the relative velocities of substitution of sodium *p*-anisate by these two substances in dilute solutions in phosphate buffers in the range pH 7—8, *i.e.*, in circumstances in which hypobromous acid ($K_a = 2{\cdot}06 \times 10^{-9}$) (cf. Shilov and Gladtchikova, *J. Amer. Chem. Soc.*, 1938, **60**, 490) would be undissociated and the aromatic substrate present as the anion. At pH 7·6 hypobromous acid gradually decomposes giving some free bromine, and so when it was used in homogeneous solution the rate of substitution was found to rise after a time. However, by working with a rapidly shaken solution containing suspended silver phosphate it was possible to obtain good second-order velocity constants until more than 75% of the material had been used; these constants corresponded to the initial velocity of the reaction in a similar solution containing no silver phosphate, which therefore acts only to regenerate hypobromous acid from aqueous bromine.

FIG. 3.

Relationship between log $k_{bi.}$ *and Hammett's acidity function* H_0 *for the bromination of benzoic acid with a sulphuric acid catalyst.*

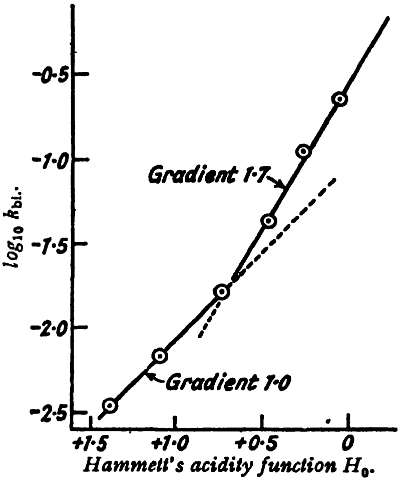
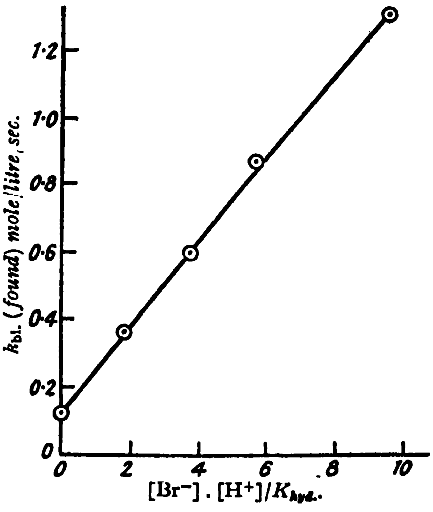


FIG. 4.

Bromination of sodium p-*anisate with hypobromous acid/bromine mixtures at* pH 7·58.



Relationship between $k_{bi.}$ *and* $[Br^-][H^+]/K_{hyd.}$

Bromine itself reacts far too rapidly with sodium *p*-anisate for it to be possible to obtain accurate velocity constants, but convincing results were obtained by adding small quantities of potassium bromide to the homogeneous hypobromous acid solutions, when, as our observations show, the equilibrium (6) is set up instantaneously. If we assume

$$HOBr + Br^- + H^+ \underset{K_{hyd.}}{\rightleftharpoons} Br_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

that this is true, and that hypobromous acid and bromine substitute concurrently, and remember that they can be titrated in exactly the same way, we can write (L):

$$\begin{aligned}\text{Velocity of substitution} &= k_{\text{bl.}}[\text{HOBr}][\text{Ar}^-]\\ &= k_{\text{HOBr}}[\text{HOBr}][\text{Ar}^-] + k_{\text{Br}_2}[\text{Br}_2][\text{Ar}^-]\\ &= [\text{HOBr}][\text{Ar}^-]\{k_{\text{HOBr}} + k_{\text{Br}_2}[\text{Br}^-][\text{H}^+]/K_{hyd.}\} \quad . \; . \; . \; . \; . \quad (\text{L})\end{aligned}$$

where $K_{hyd.} = [\text{Br}^-][\text{H}^+][\text{HOBr}]/\text{Br}_2$], the equilibrium constant for (6). The latter has been calculated as $4{\cdot}29 \times 10^{-9}$ at the temperature used (21·5°) from the equation given by Liebhafsky (*J. Amer. Chem. Soc.*, 1934, **56**, 1500; 1939, **61**, 3513).

Now substitution of an aromatic nucleus by hypobromous acid does not affect the acidity of the solution, and the reaction (7)

$$\text{Br}_2 + \text{MeO}{\cdot}\text{C}_6\text{H}_4{\cdot}\text{CO}_2^- \longrightarrow \text{Br}^- + \text{H}^+ + \text{MeO}{\cdot}\text{C}_6\text{H}_3\text{Br}{\cdot}\text{CO}_2^- \quad . \; . \; . \quad (7)$$

(i) regenerates bromide anions as the free bromine is consumed and (ii) reproduces the hydrogen ions used up in the formation of molecular bromine (equation 6), so that in our reaction system both [Br⁻] and [H⁺] remain constant. Consequently, as Fig. 4 shows, the graph of $k_{\text{bl.}}$ against the function $[\text{Br}^-][\text{H}^+]/K_{hyd.}$ gives a linear plot, from the slope of which k_{Br_2} has been evaluated as 119 mole/l./sec.

The data plotted on Fig. 4 give the ratio $k_{\text{HOBr}} : k_{\text{Br}_2}$ as 1 : 1100, and an approximate ratio of this order was also obtained in attempt to measure k_{Br_2} directly in an identical buffer solution.

However the figure for k_{HOBr} derived from the data of Fig. 4 is itself that for a composite velocity constant. Lines 1—4 of Table III show that as the normality of the phosphate buffer is increased the velocity of bromination of sodium *p*-anisoate (without added bromide) increases also, though the pH of the solution has not changed. On the other hand comparisons between lines 2*a* and 2*b*, and between lines 3*a* and 3*b* of Table III show that if the acid component of the buffer is kept in constant concentration, then, although the pH of the reacting mixture may vary in the range of pH 7—8 which does not sensibly affect the dissociation of molecular hypobromous acid, the velocity of bromination remains nearly constant.

TABLE III.

Bromination of sodium p-*anisate with bromine-free hypobromous acid in phosphate buffers at* 21·5°.

	Na_2HPO_4 M., $\times 10^{-3}$.	KH_2PO_4 M, $\times 10^{-3}$.	pH (glass electrode).	HOBr, M, $\times 10^{-3}$.	Anisate, M., $\times 10^{-3}$.	$k_{\text{bl.}}$ (found), mol./l./sec.
2*a*	1·13	2·00	7·58	4·23	7·03	0·105
1	1·13	2·00	7·58	5·04	14·06	0·112
2*b*	2·99	2·00	7·92	4·29	7·03	0·103
3*a*	2·26	4·00	7·58	4·29	7·03	0·161
3*b*	1·13	4·00	7·40	4·21	7·03	0·166
4	3·39	6·00	7·58	3·99	7·03	0·221
	No buffer salt		7·58	By extrapolation $k_{\text{bl.}} = 0{\cdot}05$		

These results can be explained, in accordance with the views of Mauger and Soper (*loc. cit.*), by supposing that there can be formed a bromine phosphate which is somewhat more reactive than undissociated hypobromous acid. Thus a change in the potassium dihydrogen phosphate concentration shifts the equilibrium (8), whilst a change of the pH at constant $[\text{H}_2\text{PO}_4^-]$

$$\text{HOBr} + \text{H}_2\text{PO}_4^- \rightleftharpoons (\text{Br}{\cdot}\text{HPO}_4)^- + \text{H}_2\text{O} \quad . \; . \; . \; . \; . \; . \; . \quad (8)$$

does not. The second dissociation constant for phosphoric acid ($K_a = 6 \times 10^{-8}$) is much greater than the dissociation constant for water, and this sequence therefore accords with Ingold's views on the relative reactivities of compounds Br—X.

The extrapolation of the experimental results of Table III shows that the value of k_{HOBr} for the bromination of sodium *p*-anisate in the absence of any buffer is of the order of 1/2000 of the value of k_{Br_2} computed from the data given in Fig. 4. This ratio is about double that of the previous estimates of Francis and of Shilov and Kaniaev, neither of whom however took such careful precautions to eliminate either effects due to acidity or effects due to small traces of free bromine.

The results of the first part of this paper show conclusively that the bromine cation is very much more reactive than molecular bromine, but since the value of the equilibrium constant for the system (1*b*) is unknown we cannot express in figures the relative reactivities of molecular and kationic bromine. Alexander (*loc. cit.*) has ascribed an appreciable brominating power to the complex anion $(\text{Br}_3)^-$. On the other hand, Bradfield, Davies, and Long (*J.*, **1949**, 1393) have shown that $(Br_3)^-$ is a much less active brominating agent than either hypobromous acid or molecular bromine; the same conclusion was reached for bromine addition by Bartlett and Tarbell (*loc. cit.*). Our results show that the ion $(Br_3)^-$ cannot play an appreciable part in the bromination of sodium *p*-anisate under our conditions of reaction, for if a concurrent substitution by this ion were concerned then the reaction velocity equation (L) (p. 570) would have to include a term

$$k_{Br_3^-} \cdot \frac{[Br^-]^2 \cdot [H^+]}{K_{Br_3^-} \cdot K_{hyd}}$$

which is of second order with respect to $[Br^-]$.

The theoretical curve for Fig. 4 would then become parabolic and not linear. The linearity of the results plotted in Fig. 4 therefore establishes that at pH 7—8 the most active brominating agent present in aqueous solutions is the simple bromine molecule, Br_2. At this acidity the concentration of the bromine cation (Br^+ or H_2OBr^+) must be quite insignificant because the substitution of sodium *p*-anisoate is not pH-dependent in slightly alkaline solution. Again, addition of bromide anion cannot in any way increase the concentration of the bromine cation in the equilibrated system (1) (p. 565), yet it does most markedly increase the rate of aromatic substitution.

Finally we would point out that in polar solvents the substitution reaction of *N*-halogeno-compounds may often be due to the formation of similar systems of cationoid reactivity (*e.g.*, 9).

$$R_2N—Br + H^+ \rightleftharpoons (R_2NH—Br)^+ \rightleftharpoons R_2NH + Br^+ \quad . \quad . \quad . \quad . \quad (9)$$

Schmid (*Helv. Chim. Acta*, 1946, **29**, 1144) for instance has found that *N*-bromosuccinimide can be used to substitute benzene and toluene in the presence of concentrated sulphuric acid. The molecular rearrangements and aromatic substitutions which can be effected by *N*-chloro- and *N*-bromo-compounds are again reactions which proceed *via* their conjugate acids, since they are dependent on general acid catalysis.

EXPERIMENTAL.

Hypobromous Acid.—Aqueous solutions of hypobromous acid were prepared by the method of Shilov and Kaniaev (*J. Gen. Chem. Russia*, 1938, **8**, 445, in Russian) by shaking *ca.* 0·08N-bromine-water, made from purified bromine, b. p. 58·1°/747 mm., with an excess of freshly prepared silver phosphate. When the smell of free bromine had disappeared (1 hour), the resulting solution was distilled from a water-bath at 40—50° under a water-pump vacuum, in an all-glass apparatus the outside of which had been covered with a heavy coat of black paint to exclude light. The condenser and receiver were both cooled in ice-water, and the latter was protected by a trap to avoid back-diffusion of impurities arising from interactions of hypobromous acid and rubber connections. The hypobromous acid solutions thus obtained were about 0·02M. and had a very pale yellow colour, most of which was due to the presence of traces of free bromine. Nearly all the latter was then removed by extracting the distillate at 0—5° with carbon disulphide-free carbon tetrachloride, and the last traces of the extractant were eliminated by centrifugation. Solutions of hypobromous acid prepared in this way give no precipitate with silver nitrate, though on storage an opalescence gradually develops. Analyses, carried out as described below, show that the product may still contain up to 2% of free bromine, but that it is almost free from bromic acid. It is reasonably stable at 0°, but, when frozen so that ice separates and the remaining liquid becomes much more concentrated, extensive decomposition occurs. Aqueous solutions which have been diluted to about 5×10^{-3}M. can be kept for about an hour at summer temperatures (20—25°) without exhibiting any change in titre or noticeable increase in free bromine content.

For the kinetic work these solutions were regularly analysed by the following methods, and allowance was made for the presence of free bromine, after it had been established that this did not react with either benzoic acid or sodium toluene-ω-sulphonate in the aqueous mixtures used.

Analytical Methods.—(i) ($HOBr + Br_2 + HBrO_3$) was determined by addition to potassium iodide in dilute sulphuric acid solution followed by thiosulphate titration. (ii) Br_2 was estimated by difference, since it did not react with benzoic acid even in strong sulphuric acid solution. 5 Ml. of the hypobromous acid reagent were run into 20 ml. of a solution of 1 g. of benzoic acid in a mixture of 40 ml. each of stabilised glacial acetic and 10N-sulphuric acids in a stoppered flask. After 6 minutes, when the HOBr had reacted completely, aliquots of this solution were run into aqueous potassium iodide, and titrated with thiosulphate. (iii) $HBrO_3$ was determined also by difference, by use of an excess of aqueous crotonic acid to remove both HOBr and Br_2, as indicated by Shilov and Kaniaev. The remaining $HBrO_3$ was allowed to liberate iodine from potassium iodide in strong hydrochloric acid in the presence of a few drops of ammonium molybdate solution, added as a catalyst. A typical analysis gave the values: HOBr, 0·018M.; Br_2, 5×10^{-4}M.; $HBrO_3$ under 4×10^{-4}M.

Quantitative Bromination of Sodium Toluene-ω-sulphonate.—Sodium toluene-ω-sulphonate (Fromm and Seixas Palma, *Ber.*, 1906, **39**, 3309) was crystallised first from hot water and then from absolute alcohol, and finally dried in a vacuum at 100°. It was neutral, stable to cold permanganate solution, and gave no precipitate with silver nitrate or barium chloride solutions. A stock solution in distilled water was mixed as required with standardised perchloric acid prepared from AnalaR chloride-free material. For kinetic measurements, freshly prepared dilute hypobromous acid was added to the prepared samples of the acidified aromatic compound contained in blackened glass-stoppered flasks immersed in a thermostat at 21·5° ± 0·05°, the initial volume regularly being 50 ml. At intervals, 5-ml. portions were withdrawn for titration with N/100-thiosulphate, by a semi-micro-burette. Since the temperature of the thermostat was very close to that of the laboratory the time of reaction could be measured to as high a degree of accuracy as that of half-addition of the mixtures to acidified potassium iodide solution. Immediately after each experiment the purity of the hypobromous acid solution was checked.

The examples in Table IV show the accuracy of the determinations of the second-order reaction velocity coefficient.

TABLE IV.

Bromination of sodium toluene-ω-sulphonate with hypobromous acid.

(*A*) $Ph\cdot CH_2\cdot SO_3Na$ = 7·09 × 10^{-3}M., HOBr = 4·73 × 10^{-3}M., $HClO_4$ = 0·0942N.

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %.	*k* (bimol.), calc.
0	0	4·59	100	—
0	37	3·37	73·5	1·306
1	11	2·68	58·4	1·263
2	10	1·89	41·2	1·268
3	58	1·10	24·0	1·286
6	2	0·66	14·4	1·279
8	20	0·41	8·9	1·154

Mean $k_{bi.}$ = 1·275 ± 0·03 mole/litre/sec.

(*B*) $Ph\cdot CH_2\cdot SO_3Na$ = 7·09 × 10^{-3}M., HOBr = 4·079 × 10^{-3}M., $HClO_4$ = 0·00942N.

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %.	*k* (bimol.), calc.
0	0	3·96	100	—
0	58	3·73	94·2	0·1477
3	15	3·26	82·3	0·1479
5	41	2·88	72·7	0·1440
8	43	2·46	62·1	0·1460
15	21	1·83	46·3	0·1448
25	25	1·23	31·1	0·1446

Mean $k_{bi.}$ = 0·146 ± 0·002 mol./litre/sec.

Quantitative Bromination of Benzoic Acid.—AnalaR benzoic acid was dissolved in purified acetic acid (Orton and Bradfield, *J.*, 1924, **125**, 960), and the solutions were diluted with the chosen specimens of dilute sulphuric or perchloric acids so that the final mixture contained 40% of acetic acid by volume. Velocity measurements were conducted at 21·5° by the procedure described above. The examples in Table V show that the bromination is strictly a second-order reaction.

TABLE V.

Bromination of benzoic acid with hypobromous acid.

(*A*) $Ph\cdot CO_2H$ = 7·876 × 10^{-3}M., HOBr = 3·747 × 10^{-3}M., H_2SO_4 = 2·352N.

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %.	*k* (bimol.), calc.
0	0	3·92	100	—
1	18	3·38	86·2	0·2503
4	35	2·44	62·2	0·2432
8	56	1·59	40·6	0·2577
12	18	1·20	30·6	0·2568
17	21	0·80	20·2	0·2580
24	14	0·48	12·2	0·2590
33	11	0·26	6·6	0·2586

Mean $k_{bi.}$ = 0·255 ± 0·004 mole/litre/sec.

(*B*) $Ph\cdot CO_2H$ = 7·876 × 10^{-2}M., HOBr = 4·035 × 10^{-3}M., $HClO_4$ = 0·1176N.

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %.	*k* (bimol.), calc.
0	0	4·14	100	—
8	12	3·43	82·8	0·00487
15	1	2·89	69·8	0·00511
20	58	2·51	60·6	0·00511
29	7	2·07	50·0	0·00511
37	43	1·69	40·8	0·00512
47	29	1·36	32·8	0·00507

Bromination of Sodium p-*Anisate with Hypobromous Acid.*—Hypobromous acid, prepared as described above, was shaken with freshly prepared silver phosphate at 0° for 4 hours, filtered through sintered glass, and added to a buffered solution of sodium *p*-anisate maintained at 21·5° in a thermostat. Table VI indicates the ensuing rate of reaction. The pH given was determined by means of a glass electrode standardised against pure potassium hydrogen phthalate.

TABLE VI.

Reaction of hypobromous acid with sodium p-*anisate at* pH 7·58.

$MeO\cdot C_6H_4\cdot CO_2Na$ = 7·03 × 10^{-3}M., HOBr = 4·20 × 10^{-3}M.

$$\left.\begin{array}{l} Na_2HPO_4 = 0{\cdot}0113\text{M.} \\ KH_2PO_4 = 0{\cdot}0020\text{M.} \end{array}\right\}\text{Buffer pH} = 7{\cdot}58.$$

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	*k* (bimol.), calc.
0	0	4·15	—
4	10	3·45	0·1105
8	27	2·58	0·1529
12	19	1·96	0·1776
17	5	1·36	0·2075
22	0	0·94	0·2339

Since solutions of hypobromous acid when stored at pH 7—8 in the absence of the aromatic reactant gradually developed a yellow colour, this increase in $k_{bi.}$ was ascribed to the slow formation of free bromine. To obviate this, a similar mixture containing silver phosphate still in suspension was agitated mechanically whilst the bromination with sodium *p*-anisate was carried out. Under these conditions the result recorded in Table VII was obtained.

TABLE VII.

Reaction of hypobromous acid with sodium p-*anisate in presence of solid silver phosphate at* pH 7·58; *temp.* 21·5°.

$MeO{\cdot}C_6H_4{\cdot}CO_2Na = 1{\cdot}406 \times 10^{-2}$M., HOBr = $5{\cdot}043 \times 10^{-3}$M.

$Na_2HPO_4 = 0{\cdot}0113$M., $KH_2PO_4 = 0{\cdot}0020$M. } Buffer pH = 7·58.

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %.	*k* (bimol.), calc.
0	0	4·98	100	—
2	1	4·08	81·9	0·1212
4	10	3·41	68·5	0·1148
6	7	2·89	58·0	0·1150
8	59	2·33	46·8	0·1127
12	52	1·78	35·7	0·1101
17	30	1·20	24·1	0·1100

Mean $k_{bi.} = 0{\cdot}113 \pm 0{\cdot}003$ mole/litre/sec.

In subsequent experiments, in which potassium bromide was added to the reaction mixtures to provide a low, but constant, concentration of bromide anions, filtered hypobromous acid solutions were used. The extrapolation of the results so obtained (cf. Fig. 4) confirms the validity of the result given in Table VII and indicates that heterogeneous catalysis does not intervene.

Table VIII indicates typical results obtained in the presence of low concentrations of bromide anions.

TABLE VIII.

Bromination of sodium p-*anisate with a hypobromous acid–bromine mixture at* pH 7·58; *temp.* 21·5°.

$MeO{\cdot}C_6H_4{\cdot}CO_2Na = 7{\cdot}03 \times 10^{-3}$M., HOBr = $4{\cdot}355 \times 10^{-3}$M., KBr = $1{\cdot}68 \times 10^{-3}$M.

$Na_2HPO_4 = 0{\cdot}0113$M., $KH_2PO_4 = 0{\cdot}002$M. } Buffer pH = 7·58 (glass electrode).

Time: min.	Time: sec.	Titre (corr. for Br_2), ml.	HOBr remaining, %.	*k* (bimol.), calc.
0	0	4·30	100	—
0	38	3·12	75·6	1·323
1	13	2·44	59·1	1·304
2	3	1·80	43·6	1·289
3	3	1·28	31·0	1·308
4	7	0·02	22·3	1·323
5	42	0·59	14·3	1·336
7	50	0·34	8·2	1·346

Mean $k_{bi.} = 1{\cdot}32 \pm 0{\cdot}02$ mole/litre/sec.

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, October 31st*, 1949.]

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108. *The Significance of the Bromine Cation in Aromatic Substitution. Part II. Preparative Applicability.*

By D. H. DERBYSHIRE and WILLIAM A. WATERS.

Acid solutions of hypobromous acid contain a very much higher concentration of bromine cations than do acid solutions of free bromine. Highly reactive solutions containing bromine cations can be made by adding mercuric or silver salts gradually to solutions of bromine in water or acetic acid in the presence of either nitric or sulphuric acid. Benzene, chlorobenzene, bromobenzene, and *p*-dibromobenzene can be brominated with such mixtures in 2N-nitric acid; benzoic acid and methyl benzoate require a stronger nitric acid solution, whilst nitrobenzene, 2 : 4-dinitrotoluene, and *m*-dinitrobenzene need 90% sulphuric acid. The expected aromatic bromination products have been isolated from these substances in 60—80% yield.

Bromine cations can also be formed by adding potassium bromate to acid solutions of bromine, and these mixtures too constitute active brominating agents.

Acetic and propionic acids, methyl alcohol, and dioxan all resist attack by bromine cations in 2N-mineral acid.

The experimental evidence substantiates the polar-activation theory of aromatic substitution.

THE kinetic evidence given in Part I (preceding paper) shows that hypobromous acid becomes a powerful brominating agent in the presence of mineral acid owing to the production of bromine cations (1),

$$H^+ + HOBr \overset{K}{\rightleftharpoons} (H_2OBr)^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and the present paper indicates the importance of this equilibrium in preparative chemistry and gives examples of its applications.

The preparation of free hypobromous acid requires such care that the reagent as such cannot conveniently be used in quantity, and, as the following calculations show, only exceedingly minute concentrations of bromine cations can be present in aqueous solutions of free bromine.

The equilibrium constant for bromine hydrolysis (2) has the low value of $4{\cdot}7 \times 10^{-9}$ at room temperature (Liebhafsky, *J. Amer. Chem. Soc.*, 1934, **56**, 1500), and consequently the

$$H_2O + Br_2 \underset{K_{hyd.}}{\rightleftharpoons} HOBr + H^+ + Br^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

degree of hydrolysis α of a bromine solution of concentration C in a medium of acidity $[H^+]$ is given by the relation

$$\alpha^2C^2[H^+]/C(1 - \alpha) = 4{\cdot}7 \times 10^{-9}$$

whence, writing $[H_2OBr^+] = K[H^+][HOBr]$ and remembering that α is small in acid solutions, we can deduce that

$$[H_2OBr^+] = \frac{\alpha C[H^+]}{K} = \text{approx.}\ \frac{7 \times 10^{-5}}{K}\sqrt{C[H^+]}$$

whilst for equivalent solutions of hypobromous acid

$$[H_2OBr^+] = C[H^+]/K$$

For M/10-solutions these two concentrations of bromine cations differ by an order of 10^4 in N-acid, and become comparable only under conditions approaching neutrality (pH *ca.* 6) in which α increases. However, in these neutral solutions $[H_2OBr^+]$ is so minute that reactions due to bromine cations can no longer be clearly detected (compare the bromination of sodium toluene-ω-sulphonate and of sodium *p*-anisate studied in Part I).

However in acid media one can easily carry out brominations by means of bromine cations by adopting the simple procedure of adding to a bromine solution a further reagent which is capable of removing bromide anions from the system. For example, if silver nitrate is added to an aqueous bromine solution then, since the solubility product of silver bromide is $7{\cdot}7 \times 10^{-13}$ at 25°, the conversion of bromine into hypobromous acid, *via* the hydrolysis (2), is so complete that we may write

$$[H_2OBr^+] = [H^+][HOBr]/K = [H^+]([Ag^+]\ \text{added})/K$$

Mercuric salts can be used in the same way, and since mercuric bromide, though un-ionised in acid media, is soluble in water the following simple experiments may be conducted to demonstrate the production and reactivity of bromine cations.

A little bromine water is added to an aqueous solution of benzene in each of two vessels. (i) To one sample dilute nitric acid is added; the solution remains of a clear orange colour. (ii) To a second sample dilute mercuric nitrate solution is added; the colour almost vanishes owing to the conversion of bromine into inactive hypobromous acid. (iii) Sample (ii) is then treated dropwise with dilute nitric acid; the bromine colour begins to reappear and the mixture soon becomes turbid owing to the separation of droplets of bromobenzene. As the reaction proceeds the colour becomes fainter again. (iv) When the acidified sample (i) is treated with mercuric nitrate solution, the bromine colour fades and droplets of bromobenzene separate.

On the preparative scale we have found that benzene can be converted into bromobenzene in 80% yield by adding silver nitrate solution dropwise to a stirred emulsion of benzene in 2N-nitric acid containing bromine. The 20% loss in yield is due to the formation of dibromobenzene. Mercuric nitrate gave a 70% yield, but the separation of the product was rather more difficult, since mercuric bromide is both slightly soluble in ether and slightly volatile. Lead nitrate was useful only for rather more reactive substances such as toluene: lead bromide is decidedly more soluble than silver bromide.

Aromatic substances which are very insoluble in water can be brominated in a similar way by using aqueous acetic acid containing either nitric or sulphuric acid. In this way we have successfully brominated chlorobenzene, bromobenzene, *p*-dibromobenzene, benzoic acid, and methyl benzoate, and have isolated in high yield the expected products of their cationoid aromatic substitution. Inactive *meta*-substituting substances, such as nitrobenzene, *m*-dinitrobenzene, and 2 : 4-dinitrotoluene do not react appreciably with the low concentrations of bromine cations that are present in 1—2N-acid, but they can all be brominated very effectively in 90% sulphuric acid by the use of silver sulphate.

Silver sulphate is soluble in concentrated sulphuric acid, and when bromine is added to such a solution the mixture merely becomes opalescent, presumably because the acidity of the solution has diminished the hydrolysis of bromine so much that the solubility product of silver bromide is not greatly exceeded. When, however, the aromatic compound is added to this mixture, silver bromide is steadily deposited as the bromination proceeds. Evidently the removal of hypobromous acid, *via* $(H_2OBr)^+$, increases the bromide anion concentration so that silver bromide can be precipitated, and this simultaneous removal of both $(H_2OBr)^+$ and (Br^-) allows the complete reaction with bromine to be effected. With *m*-dinitrobenzene however heating to 100° was necessary. In the absence of silver sulphate these inactive nitro-compounds do not react, even at 100°, with bromine in 90% sulphuric acid, but when it is added the expected bromo-derivative can easily be prepared in 60—80% yield.

Since no other method of bromination of these deactivated aromatic compounds, such as heating to a high temperature with an iron catalyst, gives comparable yields of clean material it is evident that free bromine cations must have an extremely high degree of reactivity. Nevertheless pyridine sulphate withstood attack under our conditions at 100°. It is possible that the free ion Br^+ rather than the solvated ion $(H_2OBr)^+$ may be present in these concentrated acid solutions, but we have not attempted as yet to discriminate between them. This direct experimental proof that the bromine cation will attack substances such as benzoic acid and nitrobenzene which are not attacked by molecular bromine substantiates the theory that the catalysts normally used to effect aromatic bromination do so by polar activation, *e.g.*, $Br_2 + FeBr_3 \rightleftharpoons (Br^+)(FeBr_4^-)$; their lower efficacy may perhaps indicate that ion-pairs rather than *free* bromine cations are often formed. Hence the major advantage of our new procedure may lie in the fact that the bromine cations are formed in solution and not on the surface of a solid catalyst.

The physical principle of effecting cationoid bromination by removing bromide anions from an acid solution of bromine can be applied practically in other ways than those described above. For instance in 1875 Krafft (*Ber.*, 1875, 8, 1045) noted that a mixture of bromine with potassium bromate in 33% sulphuric acid constituted a brominating agent which would readily brominate both benzene and bromobenzene at room temperature, and we have confirmed that bromine–bromate mixtures are very effective in 50% sulphuric acid. The rôle of the bromate is clearly the removal of bromide anions

$$5H^+ + 5Br^- + HBrO_3 \rightleftharpoons 3H_2O + 3Br_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and from the equilibria (1), (2), and (3) can be derived the relation

$$[H_2OBr]^+ = \text{Const.}\ [H^+][Br_2]^{\frac{2}{5}}[HBrO_3]^{\frac{1}{5}}$$

which indicates that even small concentrations of bromates should be exceedingly effective as catalysts.

It is interesting to note that the direct iodination of nitrobenzene has been effected by Masson and Hanby (*J.*, 1938, 1699) by the use of a very similar system in which they considered that iodine cations were present. Many other similar reaction mixtures for the preparation and study of the reactive cations of the halogens can now be envisaged.

It may be noted that we have, as yet, effected only the cationoid bromination of aromatic nuclei; alkyl side-chains, as in 2 : 4-dinitrotoluene, do appear not to be attacked. Though we have not attempted to carry out the cationoid bromination of saturated aliphatic molecules in concentrated sulphuric acid we have found that carefully purified specimens of acetic acid, propionic acid, methyl alcohol, and dioxan were all quite unaffected by hypobromous acid in 2N-sulphuric acid solution. In each case the drop in titre of the hypobromous acid was not detectable after an hour at 22·4°. This would appear to be a significant indication that the reaction (4) does not normally occur in aqueous solution, although it conflicts with the recent

$$H_2OBr^+ + R_3C{-}H \longrightarrow Br{-}CR_3 + H_3O^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

demonstration by Arcus, Campbell, and Kenyon (*J.*, 1949, 1510) that a Walden inversion can be brought about by an analogous exchange of ions in carbon tetrachloride solution. The discrepancy may perhaps be due to the solvation of the bromine cation and the stabilising effect of the ionising solvent on the substitution reaction as a whole.

EXPERIMENTAL.

Bromination of Benzene.—Benzene (22 ml., 0·25 mol.) and bromine (6·5 ml., 0·125 mol.) were stirred together in 1 l. of 2N-nitric acid, and 22 g. (0·125 mol.) of silver nitrate in water (100 ml.) were added gradually during 1½ hours. Light was excluded from the reaction mixture. After removal of residual bromine by sodium sulphite the product was extracted with ether, dried, and fractionated. It gave 15 g. (80% calc. on the bromine) of pure bromobenzene. Rapid addition of the silver nitrate diminished the yield and produced more dibromobenzene. In the absence of silver nitrate there was no reaction.

Brominations of Chlorobenzene, Bromobenzene, and p-*Dibromobenzene.*—Chlorobenzene (12 ml., 0·1 mol.) and bromine (5·2 ml., 0·1 mol.) were dissolved in a mixture of glacial acetic acid (300 ml.) and diluted nitric acid [50 ml. (*d* 1·4) in 100 ml. of water]. To the stirred cold mixture, silver nitrate solution (17 g. in 50 ml. of water) was added dropwise during ½ hour. The resulting solution was diluted with water (2 l.), freed from residual bromine, partly neutralised and extracted with ether. The dried extract was fractionated and the resulting *p*-chlorobromobenzene crystallised from alcohol; yield, 11 g.; m. p. 65—67°.

Bromobenzene (17 g.) was treated similarly and gave 13 g. of *p*-dibromobenzene, of m. p. and mixed m. p. 85—86°. *p*-Dibromobenzene (12 g.) was brominated similarly in a mixture of 700 ml. of acetic acid, 65 ml. of nitric acid (*d* 1·4), and 50 ml. of water at 40°. The reaction product contained an involatile residue which was separated by fractional crystallisation from ethyl alcohol into 1 : 2 : 4-tribromobenzene, m. p. 42—44°, and 1 : 2 : 4 : 5-tetrabromobenzene, m. p. 177—178°.

Bromination of Benzoic Acid and Methyl Benzoate.—Benzoic acid (13 g., 0·1 mol.) and bromine (5·2 ml., 0·1 mol.) were dissolved in a mixture of glacial acetic acid (300 ml.), concentrated nitric acid (65 ml.), and water (50 ml.), and treated dropwise, with vigorous mechanical stirring, with aqueous silver nitrate (17 g. in 100 ml. of water). The resulting solution yielded 14 g. of *m*-bromobenzoic acid, m. p. 152—154°. Methyl benzoate (16 g.) was treated similarly and the product was distilled under reduced pressure; it gave 7 g. of methyl *m*-bromobenzoate, b. p. 117—130°/20 mm., m. p. 28—30°.

Bromination of Nitrobenzene and 2 : 4-*Dinitrotoluene.*—Nitrobenzene (10 ml., 0·1 mol.) and bromine (5·2 ml., 0·1 mol.) were dissolved in a mixture of 90 ml. of concentrated sulphuric acid and 10 ml. of water, and silver sulphate (17 g., 0·1 mol.) was then added. The mixture was shaken mechanically for 16 hours, after which time the colour of the bromine had almost disappeared and silver bromide had been precipitated. The resulting solution was diluted with water, freed from remaining bromine, and extracted with ether. The dried extract solidified on cooling and gave 14·8 g. (70%) of *m*-bromonitrobenzene, m. p. and mixed m. p. 55—56°.

2 : 4-Dinitrotoluene (18·5 g., 0·1 mol.) was brominated in a similar manner during 36 hours and gave 16 g. (80%) of 6-*bromo*-2 : 4-*dinitrotoluene* which crystallised from alcohol in long pale yellow needles, m. p. 57·5—58° (Found : N, 10·6. $C_7H_5O_4N_2Br$ requires N, 10·7%). These became deep yellow on prolonged exposure to sunlight and gave a very intense reddish-purple colour when treated with acetone and aqueous potassium hydroxide. The compound was not hydrolysed when refluxed with alcoholic potassium hydroxide, and hence the bromine is neither adjacent to a nitro-group nor in the side-chain.

Bromination of m-*Dinitrobenzene.*—*m*-Dinitrobenzene (8·5 g., 0·05 mol.), bromine (3 ml.), and silver sulphate (8 g.) were dissolved in concentrated sulphuric acid (100 ml.). The mixture was left overnight without the onset of reaction; it was then heated under a reflux at 100° for 11 hours, during which silver bromide was steadily deposited. The resulting solution, after dilution with water, yielded 6·5 g. of a solid organic product which, after repeated crystallisation from alcohol, gave 5·5 g. of 1-bromo-3 : 5-dinitrobenzene of m. p. 77—78° (Found : Br, 32·0. Calc. for $C_6H_3O_4N_2Br$: Br, 32·3%). Elion (*Rec. Trav. chim.*, 1923, **42**, 145) gives m. p. 77°.

Pyridine was heated at 100° in a similar mixture for 2 days but gave no recognisable quantity of bromination product.

Bromination of Benzoic Acid with Bromine and Bromic Acid.—Benzoic acid (13 g., 0·1 mol.) and bromine (2·1 ml.) were dissolved in a mixture of glacial acetic acid (250 ml.) and concentrated sulphuric acid (150 ml.). A solution of potassium bromate (4 g. in 50 ml. of warm water) was added slowly during ½ hour, with vigorous stirring, and the temperature maintained at 25° by external cooling. Precipitation of *m*-bromobenzoic acid was noted after about 20 minutes' reaction. After the mixture had been stirred continuously for a further hour, a second, similar portion of potassium bromate solution was added slowly during ½ hour. Finally the precipitated *m*-bromobenzoic acid, m. p. 150—154° (11 g.), was collected on a sintered-glass filter, washed with a little water, and dried.

Brominations effected with Mercuric Nitrate.—(i) Benzene (15 ml.), bromine (5·2 ml.), acetic acid (400 ml.), and nitric acid [33 ml. (*d* 1·4) in 100 ml. of water] were stirred together at room temperature, and mercuric nitrate solution (17 g. in 75 ml. of water) was dropped in during ½ hour. The bromine had then disappeared. The product was diluted, partly neutralised (sodium carbonate), and repeatedly extracted with ether. The extract, when washed with alkali, dried, and fractionated, gave 10 g. (70%) of bromobenzene.

(ii) Benzoic acid (13 g., 0·1 mol.), bromine (5·2 ml.), glacial acetic acid, and nitric acid [65 ml. (*d* 1·4) and 50 ml. of water] were stirred together at about 23°, and an aqueous solution of mercuric nitrate (17 g. as above) was added during ½ hour; mercuric bromide was deposited. After a further ½ hour the solution was poured into water (2 l.), freed from bromine (sodium sulphite), and extracted with ether. The extract was freed from mercuric salts by means of hydrogen sulphide and then concentrated. From the residue 12 g. (60%) of pure *m*-bromobenzoic acid, m. p. and mixed m. p. 154—155°, were obtained by recrystallisation from alcohol–water.

The Stabilities of Some Aliphatic Compounds.—(i) *Acetic acid.* A product purified by fractional distillation from chromium trioxide, and stable both to free bromine and to potassium permanganate, was used. 20 Ml. were mixed with 20 ml. of 10N-sulphuric acid and 10 ml. of approx. 0·02N-hypobromous acid and kept in a thermostat at 17° for 20 minutes. There was no change in the potassium iodide–thiosulphate titre of the mixture.

(ii) *Propionic acid.* The acid was purified by heating 50 ml. with 2 g. of chromium trioxide on a steam-bath for 2 hours, and was finally fractionated under reduced pressure from fresh chromium trioxide. It had b. p. 55°/23 mm. and wa sstable to permanganate. A mixture of 5 ml. in 15 ml. of water, 20 ml. of 5N-sulphuric acid and 10 ml. of *ca.* 0·02N-hypobromous acid exhibited no titre change during 50 minutes' storage at room temperature.

(iii) *Methyl alcohol.* A sample, purified by refluxing with sodium hypoiodite, was distilled from silver nitrate and finally dried over quicklime and fractionated; it then had b. p. 66°/675 mm. A mixture similar to that of (ii) above showed no change in titre during 40 minutes.

(iv) *Dioxan.* 150 Ml. of dioxan, 8 ml. of bromine, and 60 ml. of 50% sulphuric acid were heated at 100° for ½ hour. Excess of bromine was removed with sulphur dioxide, and the solution was then made alkaline with aqueous potassium hydroxide. The lower aqueous layer was removed and the remaining dioxan was dried (KOH) and fractionated carefully. The pure product, b. p. 100·5°/767 mm., was stable both to cold neutral potassium permanganate solution and to an acid hypobromous acid solution similar to that used for (ii) above.

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, October 31st,* 1949.]

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109. *The Purification of Lutecium by Fractionation of Hexa-antipyrinelutecium Iodide.*

By JOSEPH K. MARSH.

It is demonstrated that fractionation of hexa-antipyrinelutecium iodide, $[Lu(C_{11}H_{12}N_2O)_6]I_3$, gives a very rapid purification. This is ascribed to a large complexing, rather than a solubility, differential. The separations of thulium and erbium, and of holmium and dysprosium, have also been noted.

THE favourable results obtainable by lanthanon tri(dimethyl phosphate) fractionation prompt a search for other compounds of a similar nature. Freed's suggestion (*J. Amer. Chem. Soc.*, 1931, **53**, 3906) that the use of non-solvated ions would permit of better fractionation than occurs with solvated ions would appear to be exemplified by the dimethyl phosphates. Few salts of the lanthanons, however, crystallise in the anhydrous state, and in these cases the metal ion appears to be complexed with some group other than water. Thus the six oxygen atoms attached to methyl groups of $Ln[PO_4Me_2]_3$ are probably complexed with the metal. The antipyrine addition compounds of the lanthanons are a noteworthy class of anhydrous salts (Kolb, *Z. anorg. Chem.*, 1913, **83**, 144; Riabtschikov and Terentieva, *Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **51**, 291), and from the solubility measurements of Wilke-Dörfurt and Schiliephake (*Z. anorg. Chem.*, 1928, **170**, 129) all the evidence points to a further resemblance to the dimethyl phosphates in that the lanthanum salts are the most soluble of the series. From published work the iodides seem most likely to constitute a favourable medium for fractionation. The solubility range is considerable, there being a 6·4-fold increase for lanthanum over the molar value for yttrium, the solubilities being 4·44 and 29·5 g./100 g. of water, respectively, at room temperature. A 26-fold increase occurs in the case of the dimethyl phosphates. The hexa-antipyrine lanthanon iodides form compact cubo-octahedral crystals, whereas the dimethyl phosphates give a fibrous pulp which generally requires filtration, thus much reducing the efficiency. Moreover, hydrolysis is too pronounced for erbium and elements of higher atomic number to be dealt with efficiently as dimethyl phosphates, whereas the antipyrine iodide compounds are stable.

By the aid of these compounds a crude lutecium product has shown a very rapid purification, and it seems probable that thulium and erbium may also be separated with reasonable efficiency. The separation of holmium and dysprosium has not proved so effective, though further work is required before it can be said definitely whether the method is useful or not, in this case.

The separation does not appear to be based upon solubility differences alone, for these are only moderate. It must depend rather upon the complexing strengths of the metals with antipyrine. The complex is much less soluble than its components, and normal lanthanon ions exist in its solution, indicating some dissociation, since oxalic acid gives the usual oxalate precipitate. The fractionation therefore is based on the crystallising out of the more strongly complexing elements. These are the more weakly basic and give slightly the less soluble complexes. Hexa-antipyrinelutecium iodide collects at the insoluble end of the series, thus providing a means of purification utilising the well-known principle that impurities are eliminated at the tail fraction preferably to the head. This is especially valuable, since lutecium is the end member of the series. The solubility of the iodide complex is such that only 10—20 g./l. of oxide are present in the fractionation series when hot, so that it is rather bulky. The solubility in methanol is considerably greater, and the same types of crystals are obtained. A mixed solvent might therefore prove useful, but a short fractionation in methanol indicated

that separation was much less pronounced in this solvent. The older methods of lutecium fractionation, by bromates or double ammonium oxalates, concentrate lutecium at the tail. The bromates are so soluble and the mother-liquors so viscous that the fractionation is difficult.

The initial fractional precipitation of some crude lutecium iodide by antipyrine gave a head fraction containing Tm_2O_3, 6·1; Er_2O_3, 0·7%, whereas the tail (fraction 9) contained 43% and 32%, respectively. Ten series of crystallisations produced a head with Tm_2O_3, 1·4%; Er_2O_3, nil; and a tail with 49% and 42%, respectively. Further work on a larger scale is in hand.

EXPERIMENTAL.

The lanthanons from a quantity of Norwegian gadolinite were fractionated by double sulphate precipitation till the oxide was free from any brown tint due to the presence of terbium. The terbium-free material was then fractionated by precipitation of basic salts till most of the yttrium had been removed but the thulium retained. The concentrate of weak bases was converted into acetate, and ytterbium removed by sodium amalgam. The residue was then fractionated as bromate, and tail fractions were taken off as soon as they became almost colourless; these consistituted the material used in this investigation.

10 G. of the crude lutecium oxide were dissolved in hydriodic acid (*d* 1·7) and excess of acid and iodine driven off on the water-bath. The salt was taken up in 400 ml. of hot water, and 20 ml. of antipyrine solution (400 g./l.) were added. A crop of hexa-antipyrinelutecium iodide was collected next day. Seven further crops were collected on subsequent days. The solution was concentrated to 100 ml. after the sixth crop, and a small residue (0·13 g. of oxide) was recovered from the final mother-liquor. After recrystallising twice, the first crop was converted into oxide (0·17 g.). The remaining crops were dissolved in boiling water, about 100 ml. being required for each. They crystallised on cooling and the mother-liquors were examined with a Beckman spectrophotometer (Model DU), thus affording an estimate of thulium and erbium present. The series was then fractionated systematically ten times in 8—10 fractions, the tail fractions being allowed to become small. Head and tail fractions were then again recovered as oxide (1·0 and 0·2 g.). The series of mother-liquors were again examined spectrophotometrically. The two sets of heads and tails were made up as chloride solutions (33·3 g./l. of oxide, except the head fraction after fractional crystallisation, which was 150 g./l.). All were examined in 1-cm. cells using the bands $\lambda\lambda$ 940, 684, and 524 mμ. for Yb, Tm, and Er estimations, respectively, checked against standard chloride solutions. In the case of the mother-liquors the assumption was made that a calibration with chloride solutions was admissible for estimating the antipyrine complex in solution. Some yellow colour had developed in fractions 13 and 14 so that here erbium estimates are probably high. The results are set out below.

Initial split.

Fraction :	3.	4.	5.	6.	7.	8.	1.	9.
Tm_2O_3	0·81	1·06	1·55	3·16	4·46	5·20 g./l.	6·1%	54%
Er_2O_3	0·20	0·40	0·60	1·22	2·31	3·80 g./l.	0·7%	32%

After ten series of crystallisations.

Fraction :	6.	7.	8.	9.	10.	11.	12.	13.	14.	5.	15.
Tm_2O_3	0·24	0·73	1·55	2·2	3·0	3·3	3·9	3·0	3·0 g./l.	1·4%	49%
Er_2O_3 ...	0·00	0·00	0·07	0·41	0·41	0·75	1·8	3·5	5·4 g./l.	nil	42%
Volume	90	90	90	70	70	70	60	30	20 ml.	2·4% of Yb_2O_3	

Holmium and Dysprosium.—A mixture of holmium and dysprosium oxides (3·5 g.) was given a similar treatment to that described above for the initial split into hexa-antipyrinelutecium iodide fractions. The first crop and final mother-liquor were recovered as oxides (0·1 g. each). The oxide of the head fraction was a deep cream, but the tail a bright brown, indicating a good concentration of terbium oxide in the tail fraction. Chloride solutions were prepared (33·3 g./l. of oxide) and examined spectrophotometrically with the following results: Ho_2O_3, Head 15·1%, Tail 7·2%. Dy_2O_3, Head 52·5%, Tail 54%.

Solubilities.—3·190 G. of mother-liquor from fraction 6 of the hexa-antipyrinelutecium iodide, after standing for 2 days at room temperature after the series of ten fractionations, were evaporated to constant weight on the water-bath and yielded 0·124 g. of solid = 4·05 g./100 g. of water; Lu_2O_3 = 4·82 g./l. A similar determination on the head fraction of the dysprosium material gave 6·15 g./100 g. of water; Dy_2O_3 = 6·86 g./l.

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110. *Dithiols. Part IV. The Reaction of Toluene-*p*-sulphonates and Methanesulphonates with Potassium Thiolacetate: A New Method for the Preparation of Thiols.*

By J. H. Chapman and L. N. Owen.

The reaction of primary toluene-*p*-sulphonates, ROTs, with potassium thiolacetate, in ethanol or acetone, provides a useful method for the preparation of thiolacetates, RSAc, and thence, by hydrolysis, of thiols.

Secondary toluene-*p*-sulphonates show wide differences in behaviour. The simple compounds, *e.g.*, the *iso*propyl ester, and certain vicinal ditoluene-*p*-sulphonates where the adjacent group is primary, *e.g.*, the ditoluene-*p*-sulphonyl derivative of propane-1 : 2-diol, react normally, though the replacement of the secondary group requires conditions more vigorous than those necessary for reaction of the primary group. In more complex substances, *e.g.*, the 3-toluene-*p*-sulphonate of 1 : 2-5 : 6-di*iso*propylidene glucose, the reaction does not occur. *cyclo*Hexyl toluene-*p*-sulphonate gives mainly *cyclo*hexene; phenyl toluene-*p*-sulphonate is non-reactive.

Several methanesulphonates have been examined and, with one exception, their reactions follow the same course as with the corresponding toluene-*p*-sulphonates, but the yields are inferior.

The difference in reactivity between primary and secondary toluene-*p*-sulphonates in the exchange reaction has been used to establish the structure of the *2-toluene-*p*-sulphonate 1-benzoate* of propane-1 : 2-diol (*2-toluene-*p*-sulphonyloxypropyl 1-benzoate*.)

In connection with the preparation of dithiols with potential antiarsenical pharmacological properties (cf. Part III; Evans, Fraser, and Owen, *J.*, 1949, 248) it occurred to us that the well-known reactivity of toluene-*p*-sulphonates might be applied to the formation of thiolacetates by carrying out an exchange reaction with potassium thiolacetate :

$$\text{ROTs} + \text{AcSK} \longrightarrow \text{RSAc} + \text{TsOK} \quad (\text{Ts} = \text{toluene-}p\text{-sulphonyl})$$

Some encouragement for this supposition was afforded by the earlier observations of Gilman and Beaber (*J. Amer. Chem. Soc.*, 1925, **47**, 1449) and of Raymond (*J. Biol. Chem.*, 1934, **107**, 85), who had shown that toluene-*p*-sulphonates react with the alkali-metal derivatives of aliphatic and aromatic thiols to give sulphides. Furthermore, the preparation of carbohydrate thiocyanates, by reaction of the toluene-*p*-sulphonates with potassium thiocyanate, had been recorded by Müller and Wilhelms (*Ber.*, 1941, **74**, 698) and by Carson and Maclay (*J. Amer. Chem. Soc.*, 1948, **70**, 2220).

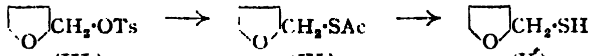
Such a reaction, if successful, would provide a useful method for the conversion of a hydroxyl group into a thiol group by the sequence ROH $\longrightarrow$ ROTs $\longrightarrow$ RSAc $\longrightarrow$ RSH, and might be of particular value for the preparation of certain polyhydroxy-thiols where the corresponding halogen derivatives (necessary for the older method involving R·Hal $\longrightarrow$ RSAc) are not easily accessible. In the carbohydrate field, for example, relatively few halogen derivatives are known, whereas a large number of toluene-*p*-sulphonates are readily available.

Since the reactivity of sulphonyl esters is markedly affected by the nature of the esterifying group, particularly by its primary or secondary character (cf. Clarke and Owen, *J.*, 1949, 315; Owen and Robins, *ibid.*, pp. 320, 326; and references there cited), it was necessary to study the reaction with potassium thiolacetate by the use of several types of compounds. The majority of these were toluene-*p*-sulphonates, but in view of the increasing interest in methanesulphonyl derivatives some of the latter were also investigated. Many of the starting materials were previously known compounds, and were prepared by standard methods; some, however, were new or exhibited some points of interest. *2-Methoxyethyl methanesulphonate*, *propylene* 1 : *2-dimethanesulphonate*, and *propylene* 1 : *2-ditoluene-*p*-sulphonate* were prepared by treatment of the corresponding hydroxy-compounds with the appropriate sulphonyl chloride in pyridine. *3-Acetoxypropylene* 1 : *2-ditoluene-*p*-sulphonate* was obtained by reaction of 2 : 3-dibromopropyl acetate with silver toluene-*p*-sulphonate. In an attempt to prepare a monotoluene-*p*-sulphonate of propane-1 : 2-diol, propylene oxide was treated with toluene-*p*-sulphonic acid in dry ether; an oily product was obtained, which by benzoylation gave a solid, separable by fractional crystallisation into two substances, m. p.s 105° and *ca.* 79°. The latter was eventually shown, by reaction with potassium thiolacetate, to be a mixture of the isomeric compounds (I) (identical with the substance of m. p. 105°) and (II), which could not readily be separated by further fractional crystallisation.

Preliminary experiments showed that the toluene-*p*-sulphonyloxy- and the methanesulphonyloxy-residues, particularly when primary, were readily replaceable by the acetylthio-group. Benzyl toluene-*p*-sulphonate showed exceptional reactivity; when it was dissolved in cold alcoholic potassium thiolacetate a precipitate of potassium toluene-*p*-sulphonate began to form almost immediately, and the reaction was complete within 15 minutes at room temperature. In general, however, the replacement was carried out by heating the reaction mixture in ethanol or acetone under reflux, using about twice the theoretical quantity of potassium thiolacetate; in many cases this excess is unnecessary for general preparative purposes, but was used in the present experiments in order that the yields of thiolacetates could be determined, under comparable conditions, for all the substances used. Potassium thiolacetate is readily soluble in ethanol, and the solid precipitated during the reactions in this solvent was almost pure potassium toluene-*p*-sulphonate. The reagent, however, is only sparingly soluble in acetone, and, since it was found to be unnecessary to use the large amount of solvent which would have been required to give complete solution, the solid remaining after completion of the reactions in acetone was a mixture of potassium toluene-*p*-sulphonate and unchanged potassium thiolacetate. All the primary compounds, and some secondary, gave the corresponding thiolacetates under these conditions, usually in good yield. With the primary compounds the reaction mixture became only slightly discoloured during the heating, but a deep red colour developed when secondary compounds were used. Hydrolysis of the thiolacetates afforded the free thiols.

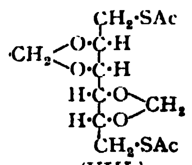
$CH_3{\cdot}CH(OTs){\cdot}CH_2{\cdot}O{\cdot}COPh \longrightarrow CH_3{\cdot}CH(SAc){\cdot}CH_2{\cdot}O{\cdot}COPh$
(I.) (XIV.)

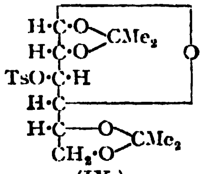
$CH_3{\cdot}CH(O{\cdot}COPh){\cdot}CH_2{\cdot}OTs \longrightarrow CH_3{\cdot}CH(O{\cdot}COPh){\cdot}CH_2{\cdot}SAc$
(II.) (XV.)

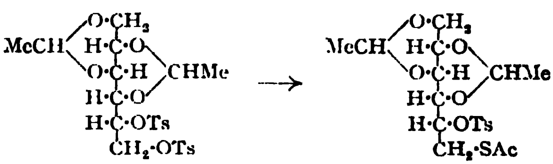

(III.) (IV.) (V.)

$CH_2(OR){\cdot}CH_2{\cdot}OTs \longrightarrow CH_2(OR){\cdot}CH_2{\cdot}SAc$
(VI.) (VII.)

$CH_2(OTs){\cdot}CH(OTs){\cdot}CH_2{\cdot}OAc \longrightarrow CH_2(SAc){\cdot}CH(SAc){\cdot}CH_2{\cdot}OAc$
(X.) (XI.)


(VIII.)


(IX.)


(XII.) (XIII.)

Tetrahydrofurfuryl toluene-*p*-sulphonate (III), in contrast to benzyl toluene-*p*-sulphonate, reacted only slowly at room temperature, but in the boiling solvent (acetone or ethanol) it gave a good yield of tetrahydrofurfuryl thiolacetate (IV). Alkaline hydrolysis of the latter readily gave *2-mercaptomethyltetrahydrofuran* (*tetrahydrofurylmethanethiol*) (V), though acid hydrolysis furnished only a small yield of the thiol, probably owing to simultaneous ring-fission. Tetrahydrofurfuryl methanesulphonate reacted much less readily than the toluene-*p*-sulphonate, and a longer period of heating was necessary. This observation is of interest in that a reverse order of reactivity is shown by these sulphonates in their reactions with potassium cyanide (Zief, Fletcher, and Kirshen, *J. Amer. Chem. Soc.*, 1946, **68**, 2743); furthermore, earlier investigators have usually reported a greater reactivity for the methansulphonates in reactions with, *e.g.*, sodium iodide (*inter al.*, Helferich and Gnüchtel, *Ber.*, 1938, **71**, 712).

n-Propyl toluene-*p*-sulphonate gave a better yield of *n*-propyl thiolacetate when acetone, rather than ethanol, was used, and it is probable that with the simple sulphonates of low molecular weight the competitive etherification reaction ROTs + EtOH ⟶ ROEt, when ethanol is used as a solvent, results in a diminished yield of thiolacetate; this was particularly apparent in the reaction with *iso*propyl toluene-*p*-sulphonate (see below).

Trimethylene ditoluene-*p*-sulphonate gave an excellent yield of the bisthiolacetate, and thence, by hydrolysis, 1 : 3-dimercaptopropane was obtained.

The possible effect of a neighbouring ether group was investigated by reactions using

2-methoxyethyl toluene-*p*-sulphonate (VI; R = Me) and methanesulphonate; *2-methoxyethyl thiolacetate* (VII; R = Me) was obtained in each case, but again the methanesulphonate was the less reactive. Hydrolysis of the product gave *2-methoxyethanethiol*. Similarly, 2-phenoxyethyl toluene-*p*-sulphonate (VI; R = Ph) gave an almost quantitative yield of *2-phenoxyethyl thiolacetate* (VII; R = Ph), and thence a high yield of *2-phenoxyethanethiol*. 2-Benzoyloxyethyl toluene-*p*-sulphonate (VI; R = COPh) afforded an example of a substance with a neighbouring ester group; it gave *2-benzoyloxyethyl thiolacetate* (VII; R = COPh), hydrolysed to 2-hydroxyethanethiol (2-mercaptoethanol). 1 : 6-Ditoluene-*p*-sulphonyl 2 : 3-4 : 5-dimethylene mannitol yielded 1 : 6-diacetyl 2 : 3-4 : 5-dimethylene 1 : 6-dithiomannitol [VIII; position of methylene residues not finally established (compare Haworth and Wiggins, *J.*, 1944, 61)].

Of the secondary toluene-*p*-sulphonates, the *iso*propyl ester reacted readily in boiling ethanol but, although potassium toluene-*p*-sulphonate was formed to the extent of 80% of the theoretical in 30 minutes, the yield of propane-2-thiol was only 6%; no propylene could be detected, and the main product was probably ethyl *iso*propyl ether, since a much better yield of thiolacetate was obtained in acetone solution. With *cyclo*hexyl toluene-*p*-sulphonate, on the contrary, poor yields of *cyclo*hexyl thiolacetate were obtained both in ethanol and in acetone, *cyclo*hexene being formed in each case; this elimination reaction is not unexpected, in view of similar results which have been observed when secondary alicyclic toluene-*p*-sulphonates are treated with a variety of reagents (Hückel, Neunhoeffer, Gercke, and Frank, *Annalen*, 1930, **477**, 143; Clarke and Owen, *loc. cit.*; Owen and Robins, *locc. cit.*). 3-Toluene-*p*-sulphonyl 1 : 2-5 : 6-di*iso*propylidene glucose (IX) failed to react with potassium thiolacetate in acetone at 110°.

The ditoluene-*p*-sulphonates of propane-1 : 2-diol and of 2 : 3-dihydroxypropyl acetate (X) provided examples of compounds containing vicinal primary and secondary sulphonyloxy-groups. In acetone solution, the primary and the secondary groups in both compounds were replaced, to give moderate yields of 1 : 2-bisacetylthiopropane and 2 : 3-bisacetylthiopropyl acetate ("BAL" triacetate) (XI), respectively. The dimethanesulphonate of propane-1 : 2-diol was somewhat less reactive than the corresponding ditoluene-*p*-sulphonate, but gave the same product as the latter. In striking contrast was the behaviour of the 5 : 6-ditoluene-*p*-sulphonate of 1 : 3-2 : 4-diethylidene sorbitol (XII) in which, even after vigorous treatment, only the primary group could be replaced, to give *6-acetyl 5-toluene-*p*-sulphonyl* 1 : 3-2 : *4-diethylidene 6-thiosorbitol* (XIII). The corresponding 5 : 6-dimethanesulphonate appeared to undergo some reaction, but gave no recognisable product.

The only aryl compound studied, phenyl toluene-*p*-sulphonate, failed to react with potassium thiolacetate.

The results are summarised in the table, in which the yields refer to distilled or crystalline thiolacetates. It is clear from these experiments that the reaction of primary toluene-*p*-sulphonates with potassium thiolacetate provides a good method for the preparation of primary thiolacetates, and thence of the corresponding thiols, but that the behaviour of a secondary toluene-*p*-sulphonyloxy-group is capable of wide variation, ranging from non-reactivity to comparatively smooth replacement, with the possibility also of the occurrence of an elimination reaction and formation of an unsaturated product. The course taken in any particular case depends on the molecular environment, and the structural factors concerned merit further study, particularly since comparable variations are already known to occur in the reactions of secondary toluene-*p*-sulphonates with other reagents, *e.g.*, potassium acetate, sodium iodide. An interesting example of a carbohydrate derivative possessing two reactive secondary methanesulphonyl groups is discussed in Part V (following paper).

These experiments demonstrated a marked difference in reactivity between primary and secondary sulphonyloxy-groups, and thus provided a novel means of investigating the structures of the toluene-*p*-sulphonate–benzoates of propane-1 : 2-diol, m. p.s 105° and 79°, to which reference was made above. When the lower-melting material was boiled with potassium thiolacetate in acetone for an hour, a mixture was obtained, consisting of a liquid thiolacetate–benzoate, together with the crystalline toluene-*p*-sulphonate–benzoate, m. p. 105°. The latter was recovered almost quantitatively after further treatment under the same conditions, but under more vigorous conditions it reacted slowly to give a different thiolacetate–benzoate. It follows from these differences in reactivity that the compound of m. p. 105° contains a secondary toluene-*p*-sulphonyl group, and must therefore be the *2-toluene-*p*-sulphonate 1-benzoate* (I); the material of m. p. 79° is evidently a mixture of (I) with the isomeric 1-toluene-*p*-sulphonate 2-benzoate (II). During the short period of reaction the latter is converted into the *2-benzoate*

1-*thiolacetate* (XV), whilst (I) is unaffected; more drastic treatment subsequently converts (I) into the 1-*benzoate* 2-*thiolacetate* (XIV). Independent confirmation of the structure of (I) has been provided by Mr. G. A. Haggis (unpublished work), who has shown that on reaction with sodium iodide, followed by hydrogenation, it gives *n*-propyl benzoate.

The reaction of sulphonic esters with potassium thiolacetate.

(Ts = toluene-*p*-sulphonate; Ms = methanesulphonate.)

Ester.	Solvent.	Time at b. p., hrs.	Yield of thiolacetate, %.
Benzyl Ts	EtOH	1	79
Tetrahydrofurfuryl Ts	EtOH	1	71
	Me_2CO	1	69
Tetrahydrofurfuryl Ms	Me_2CO	1	20
	Me_2CO	6	60
n-Propyl Ts	EtOH	0·5	55
	Me_2CO	0·5	72
Propane-1 : 3-diol di-Ts	EtOH	1	88
2-Methoxyethyl Ts	EtOH	1	67
	Me_2CO	1	69
2-Methoxyethyl Ms	Me_2CO	1	56
2-Phenoxyethyl Ts	EtOH	1	92
2-Benzoyloxyethyl Ts	EtOH	1	70
2 : 3 : 4 : 5-Dimethylene mannitol 1 : 6-di-Ts	Me_2CO	6	89
*iso*Propyl Ts	EtOH	0·5	6
	Me_2CO	2	49
	Me_2CO	6	71
*cyclo*Hexyl Ts	EtOH	0·25	19
1 : 2-5 : 6-Di*iso*propylidene glucose 3-Ts	Me_2CO	18 *	0
Propane-1 : 2-diol di-Ts	Me_2CO	6	50
	Me_2CO	8	60
	Me_2CO	12	58
Propane-1 : 2-diol di-Ms	Me_2CO	4	38
	Me_2CO	6	43
Propane-1 : 2-diol 1-benzoate 2-Ts	Me_2CO	15 *	56
2 : 3-Dihydroxypropyl acetate di-Ts	Me_2CO	8	68
1 : 3-2 : 4-Diethylidene sorbitol 5 : 6-di-Ts	Me_2CO	6	87 †
1 : 3-2 : 4-Diethylidene sorbitol 5 : 6-di-Ms	Me_2CO	6	0
1 : 3-2 : 4-Diethylidene sorbitol 6-thiolacetate 5-Ts	Me_2CO	15 *	0
Phenyl Ts	Me_2CO	18 *	0

* Reaction at 110°. † Primary group only.

EXPERIMENTAL.

(M. p.s were determined on the Koefler block, and are corrected.)

Preparation of the Sulphonic Esters.—The following were made by published methods: benzyl toluene-*p*-sulphonate, m. p. 58° (Tipson, *J. Org. Chem.*, 1944, **9**, 235); tetrahydrofurfuryl toluene-*p*-sulphonate, m. p. 37—38°, after distillation at 110° (bath)/0·0001 mm. (Barger, Robinson, and Urushibara, *J.*, 1937, 714; also obtained by the general method of Tipson, *loc. cit.*); tetrahydrofurfuryl methanesulphonate, b. p. 116°/1 mm., n_D^{18} 1·4613 (Zief, Fletcher, and Kirshen, *loc. cit.*); 2-methoxyethyl toluene-*p*-sulphonate, b. p. 120—130°/0·1 mm. (Tipson, *loc. cit.*); 2-phenoxyethyl toluene-*p*-sulphonate, m. p. 81° (Tipson, *loc. cit.*); 2 : 3 : 4 : 5-dimethylene mannitol 1 : 6-ditoluene-*p*-sulphonate, m. p. 164° (Haworth and Wiggins, *J.*, 1944, 61); *cyclo*hexyl toluene-*p*-sulphonate, m. p. 43° (Hückel, Neunhoeffer, Gercke, and Frank, *loc. cit.*); 1 : 2-5 : 6-di*iso*propylidene glucose 3-toluene-*p*-sulphonate, m. p. 120° (Freudenberg and Ivers, *Ber.*, 1922, **55**, 929); phenyl toluene-*p*-sulphonate, m. p. 95° (Reverdin and Crépieux, *Ber.*, 1902, **35**, 1443).

n-Propyl toluene-*p*-sulphonate was prepared by treatment of *n*-propanol (30 g.) in pyridine (250 c.c.) with toluene-*p*-sulphonyl chloride (105 g.) at −5° until all the chloride had dissolved, followed by 4 hours at 0°. The solution was then poured into ice-cold 5N-sulphuric acid (750 c.c.), and the oil was taken up in chloroform; the extract was washed with 2N-sulphuric acid and with sodium hydrogen carbonate solution, dried (K_2CO_3), and evaporated to an oil. The product (88 g., 82%) distilled at b. p. 134°/0·4 mm., n_D^{20} 1·5069.

The propylene 1 : 3-ditoluene-*p*-sulphonate was obtained from the diol (8 g.), toluene-*p*-sulphonyl chloride (44 g.), and pyridine (175 c.c.). After 1 hour at 0°, addition of 5N-sulphuric acid precipitated the ester as a solid, which formed plates, m. p. 92°, from methanol; yield, 27 g. (70%) (Found: C, 53·4; H, 5·2. Calc. for $C_{17}H_{20}O_6S_2$: C, 53·1; H, 5·25%) (cf. King, *J.*, 1928, 2426).

2-Benzoyloxyethyl toluene-*p*-sulphonate was prepared from 2-benzoyloxyethanol (Cretcher and Pittenger, *J. Amer. Chem. Soc.*, 1925, **47**, 2560) by a modification of the method of Butler *et al.* (*ibid.*, 1935, **57**, 575). The alcohol (20 g.), toluene-*p*-sulphonyl chloride (11·5 g.), and pyridine (100 c.c.), after being mixed at 0°, were kept at room temperature for 4 hours, and gave 23·6 g. (61%) of the ester (Butler *et al.*, *loc. cit.*, using less pyridine, recorded a yield of 26%).

Treatment of 2-methoxyethanol (10 g.) in pyridine (100 c.c.) with methanesulphonyl chloride

(16·6 g.), below −5° and then 12 hours at *ca.* 15°, dilution with water, and extraction of the product with chloroform, gave *2-methoxyethyl methanesulphonate* (14·6 g., 72%), b. p. 80°/0·4 mm., n_{D}^{20} 1·4314 (Found: C, 31·1; H, 6·5. $C_4H_{10}O_4S$ requires C, 31·15; H, 6·55%).

*iso*Propyl toluene-*p*-sulphonate, n_{D}^{20} 1·5040, was prepared in the same way as the *n*-propyl ester.

Treatment of propane-1 : 2-diol (5 g.) in pyridine (150 c.c.) with toluene-*p*-sulphonyl chloride (28 g.) at 0° for 1 hour and at room temperature overnight gave, on pouring of the mixture into dilute sulphuric acid, a precipitate of the *ditoluene*-p-*sulphonate*, which crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 68—69° (Found: C, 53·0; H, 4·95. $C_{17}H_{20}O_6S_2$ requires C, 53·1; H, 5·25%). The *dimethanesulphonate*, prepared in a similar way, crystallised from the same solvent in rectangular tablets, m. p. 53° (Found: C, 25·85; H, 5·25. $C_5H_{12}O_6S_2$ requires C, 25·85; H, 5·2%).

2 : 3-*Ditoluene*-p-*sulphonyloxypropyl acetate* was obtained by heating under reflux a solution of 2 : 3-dibromopropyl acetate (10 g., b. p. 130°/32 mm.; n_{D}^{21} 1·5060) in benzene (100 c.c.) with silver toluene-*p*-sulphonate (25 g.) for 15 hours. The filtered solution was then washed with aqueous sodium hydrogen carbonate, and evaporated to an oil, which crystallised on addition of light petroleum and formed needles (5·45 g., 32%), m. p. 100°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 51·5; H, 5·1. $C_{19}H_{22}O_8S_2$ requires C, 51·55; H, 5·0%).

The dimethane sulphonate of 1 : 3-2 : 4-diethylidene sorbitol was obtained by the method described in Part VII. The corresponding ditoluene-*p*-sulphonate was prepared by addition of toluene-*p*-sulphonyl chloride (8·95 g.) to a solution of 1 : 3-2 : 4-diethylidene sorbitol (5 g.) in pyridine (20 c.c.) at 0°. After 12 hours at *ca.* 5°, addition of water gave the solid derivative (7·9 g.), m. p. 173°, $[\alpha]_{\mathrm{D}}^{20}$ − 11·2° (*c*, 1 in chloroform), after recrystallisation from methanol (cf. Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837; Wiggins, *J.*, 1946, 388).

Reaction of Propylene Oxide with Toluene-p-*sulphonic Acid.*—To a solution of the oxide (9 g.) in dry ether (150 c.c.), dry toluene-*p*-sulphonic acid (27 g., 1 mol.) was added in small portions, and the solution was then kept overnight. During this time a lower oily layer was formed. The solvent was removed under reduced pressure, and the residual oil was dissolved in chloroform, washed with water and with sodium hydrogen carbonate solution, and dried. Evaporation of the solvent then gave a pale yellow viscous oil (33 g.). This was dissolved in pyridine (150 c.c.) and treated with benzoyl chloride (25 g.), with cooling. After 1 hour at 15°, water was added, and the precipitated oil was taken up in chloroform and washed with dilute sulphuric acid, sodium hydrogen carbonate, and finally with water. The dried solution was then evaporated, and gave a semi-solid residue. One recrystallisation from benzene–light petroleum (b. p. 60—80°) gave 35 g. of material, m. p. *ca.* 70—75°, from which, by several recrystallisations from methanol, *2-toluene*-p-*sulphonyloxypropyl 1-benzoate* was obtained; it formed needles or plates, m. p. 105° (Found: C, 61·4; H, 5·7. $C_{17}H_{18}O_5S$ requires C, 61·05; H, 5·4%). The main portion of the reaction product, recovered from the mother-liquors, was a mixture of the structural isomers; after repeated crystallisations from benzene–light petroleum or from methanol it gave colourless needles, m. p. *ca.* 79° (Found: C, 60·8; H, 5·6%).

Reaction of Sulphonic Esters with Potassium Thiolacetate.—The conditions for each experiment are given individually below, and the yields of thiolacetates are summarised in the table. Except where otherwise stated, reaction products were worked up by the following procedure. The cooled mixture was filtered, and the salts were washed with cold solvent. The ethanol or acetone filtrate and washings were concentrated to small bulk and then diluted with water. The product, if solid, was collected, washed, and recrystallised; if liquid, it was extracted with ether, the extracts were washed with water, then dried and evaporated, and the residual oil was purified by distillation.

Hydrolysis of Thiolacetates to Thiols.—(a) *Alkaline hydrolysis.* The thiolacetate was dissolved in cold 5% methanolic potassium hydroxide (2·1 mols. of KOH per acetylthio-group) and left overnight, under nitrogen, at room temperature. A slight excess of hydrochloric acid was then added, with cooling, and after removal of methanol under reduced pressure the thiol was isolated by ether-extraction.

(b) *Acid hydrolysis.* The thiolacetate was dissolved in ten times its weight of N-methanolic hydrogen chloride and boiled under reflux for 4 hours under nitrogen. The cooled solution was then diluted with water, concentrated under reduced pressure to remove methanol, and extracted with ether to obtain the thiol.

The yields of thiol, recorded below in the individual cases, are based on thiolacetates, and are not overall yields.

Quantitative Determination of Thiol Values.—The method described in Part II (Evans and Owen, *J.*, 1949, 244) was used, except that with non-water-soluble thiols sufficient methanol was added to effect dissolution in the hydrochloric acid before titration with iodine.

Benzyl Thiolacetate.—(*a*) Benzyl toluene-*p*-sulphonate (1 g.) and potassium thiolacetate (1 g.) were separately dissolved in the minimum amount of ethanol. On mixing of the cold solutions, a copious white precipitate was formed within a few minutes. After 10 minutes, the potassium toluene-*p*-sulphonate (0·6 g., 75%) was filtered off and washed with cold ethanol.

(*b*) The toluene-*p*-sulphonate (5 g.) and potassium thiolacetate (5 g.) were heated in ethanol (250 c.c.) under reflux, and gave benzyl thiolacetate (2·5 g.), b. p. 54°/0·05 mm., n_{D}^{20} 1·5578, which on acid hydrolysis furnished toluene-ω-thiol, b. p. 100°/22 mm. (Found: thiol S, 25·4. Calc. for C_7H_8S: S, 25·8%).

Tetrahydrofurfuryl Thiolacetate.—The toluene-*p*-sulphonate reacted only slowly with potassium thiolacetate in ethanol at room temperature, replacement being incomplete after 10 days. The toluene-*p*-sulphonate (14 g.) or the methanesulphonate (6 g.), with potassium thiolacetate (12·5 g. or 7·5 g. respectively), on being heated under reflux, in acetone or ethanol (100 c.c.), gave the *thiolacetate*, b. p. 107°/16 mm., n_{D}^{20} 1·4941 (Found: C, 52·4; H, 7·65. $C_7H_{12}OS$ requires C, 52·5; H, 7·55%). Light absorption: max. 2300 A., ε 4800. Alkaline hydrolysis then gave *2-mercaptomethyltetrahydrofuran* (55%), b. p. 113°/145 mm., n_{D}^{20} 1·4910 (Found: C, 50·5; H, 8·8; thiol S, 26·7. $C_5H_{10}OS$ requires C, 50·8; H, 9·1; S, 27·1%). The *phenylurethane*, prepared by treatment of the thiol with a slight excess of phenyl *iso*cyanate for 4 days at room temperature, crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 99° (Found: N, 6·1. $C_{12}H_{15}O_2NS$ requires N, 5·9%).

n-*Propyl Thiolacetate.*—The toluene-*p*-sulphonate (10 g.), potassium thiolacetate (11 g.), and acetone (100 c.c.) were heated under reflux, and gave the thiolacetate (4 g.), b. p. 141°, n_D^{20} 1·4590 (Wallach and Bleibtreu, *Ber.*, 1879, **12**, 1062, give b. p. 135—137°).

1 : 3-*Bisacetylthiopropane.*—The ditoluene-*p*-sulphonate of propane-1 : 3-diol (9 g.) and potassium thiolacetate (10·5 g.) were heated under reflux in ethanol (200 c.c.), and gave the bisthiolacetate (4 g.), b. p. 152°/24 mm., n_D^{24} 1·5209, which on acid hydrolysis furnished propane-1 : 3-dithiol (57%), b. p. 110°/120 mm., n_D^{21} 1·5380 (Found : thiol S, 59·1. Calc. for $C_3H_8S_2$: S, 59·3%).

2-*Methoxyethyl Thiolacetate.*—The toluene-*p*-sulphonate (10 g.) or the methanesulphonate (8·4 g.) was treated with potassium thiolacetate (10 g. or 13·5 g., respectively) in the boiling solvent (100 c.c.). The *thiolacetate* had b. p. 110°/110 mm., n_D^{18} 1·4645 (Found : C, 44·7; H, 7·45. $C_5H_{10}O_2S$ requires C, 44·8; H, 7·55%). Light absorption : max. 2280 A., ε 2600.

Hydrolysis of the thiolacetate (8 g.) under acid conditions gave, on evaporation of the solvent, no thiol; owing to its volatility in methanol it was present in the distillate, which was therefore made alkaline by the addition of 10% methanolic potassium hydroxide (70 c.c.) and evaporated to dryness under nitrogen. The residue was acidified with concentrated hydrochloric acid and extracted with ether. The dried extract was evaporated, the ether being removed through a 10″ Vigreux column, and the residue on distillation gave 2-*methoxyethanethiol* (3 g., 55%), b. p. 112°, n_D^{23} 1·4488 (Found : C, 39·75; H, 9·0; thiol S, 34·1. C_3H_8OS requires C, 39·1; H, 8·75; S, 34·8%).

Treatment of the thiol (42 mg.) with 1-chloro-2 : 4-dinitrobenzene (100 mg.) and 2% aqueous sodium hydroxide (1·0 c.c.) in boiling ethanol (10 c.c.) for 10 minutes, followed by addition of water, gave 2 : 4-*dinitrophenyl 2-methoxyethyl sulphide* (95 mg.), which crystallised from ethanol in bright yellow plates, m. p. 90° (Found : N, 10·95. $C_9H_{10}O_5N_2S$ requires N, 10·85%).

2-*Phenoxyethyl Thiolacetate.*—The toluene-*p*-sulphonate (10 g.) and potassium thiolacetate (8 g.) in boiling ethanol (150 c.c.) gave the *thiolacetate*, which crystallised from methanol in plates, m. p. 48° (Found : C, 61·4; H, 6·4. $C_{10}H_{12}O_2S$ requires C, 61·4; H, 6·2%). On acid hydrolysis it gave 2-phenoxyethanethiol (90%), b. p. 134°/29 mm., n_D^{23} 1·5597 (Found : C, 62·3; H, 6·4; thiol S, 20·6. $C_8H_{10}OS$ requires C, 62·3; H, 6·5; S, 20·8%); the *phenylurethane* of this thiol formed needles, m. p. 113°, from light petroleum (b. p. 60—80°) (Found : N, 5·3. $C_{15}H_{15}O_2NS$ requires N, 5·15%).

2-*Benzoyloxyethyl Thiolacetate.*—The toluene-*p*-sulphonate (10 g.) and potassium thiolacetate (7 g.) were heated under reflux in ethanol (150 c.c.). The thiolacetate (4·7 g.) had b. p. 117°/0·1 mm., n_D^{20} 1·5446 (Found : C, 58·5; H, 5·4. $C_{11}H_{12}O_3S$ requires C, 58·9; H, 5·4%). On acid hydrolysis, 2-hydroxyethanethiol (52%), b. p. 65°/17 mm., was obtained, and was characterised as the bisphenylurethane, m. p. and mixed m. p. with an authentic sample, 146°.

1 : 6-*Diacetyl* 2 : 3-4 : 5-*Dimethylene* 1 : 6-*Dithiomannitol.*—The ditoluene-*p*-sulphonate (1 g.) was treated with potassium thiolacetate (0·9 g.) in boiling acetone (25 c.c.). The solid product, recrystallised from aqueous ethanol, furnished colourless needles of the *bisthiolacetate*, m. p. 109°, $[\alpha]_D^{20}$ +187° (*c*, 1·2 in chloroform) (Found : C, 44·8; H, 5·6; S, 19·8. $C_{12}H_{18}O_6S_2$ requires C, 44·7; H, 5·6; S, 19·9%). Light absorption : max. 2290 A., ε 11,000.

iso*Propyl Thiolacetate.*—The toluene-*p*-sulphonate (10 g.), in boiling ethanol or acetone (100 c.c.), was treated with potassium thiolacetate (11 g.), and gave *iso*propyl thiolacetate, b. p. 123°, n_D^{20} 1·4528 (Wallach and Bleibtreu, *loc. cit.*, give b. p. 124—127°).

cyclo*Hexyl Thiolacetate.*—When *cyclo*hexyl toluene-*p*-sulphonate (10 g.) and potassium thiolacetate (9 g.) were heated under reflux in ethanol (50 c.c.), a rapid reaction occurred and the mixture became deep red; after being heated for 15 minutes, it was worked up and gave 8·15 g. (98%) of potassium toluene-*p*-sulphonate. The solvent was removed through a 12″ Vigreux column, and the first runnings contained much *cyclo*hexene, identified by its characteristic odour and unsaturation towards bromine. The small residue, on distillation, gave *cyclo*hexyl thiolacetate (1·2 g.), b. p. 130°/110 mm., n_D^{20} 1·5091 (Cunneen, *J.*, 1947, 134, gives b. p. 90°/14 mm.).

1 : 2-*Bisacetylthiopropane.*—The ditoluene-*p*-sulphonate or dimethanesulphonate of propane-1 : 2-diol (10 g.) was heated with potassium thiolacetate (6 g. or 10 g., respectively) in acetone (100 c.c.), and gave the bisthiolacetate, b. p. 93°/1 mm., n_D^{21} 1·5197 (Found : C, 43·45; H, 6·25. $C_7H_{12}O_2S_2$ requires C, 43·7; H, 6·3%).

2 : 3-*Bisacetylthiopropyl Acetate.*—The toluene-*p*-sulphonate (5 g.) and potassium thiolacetate (6·5 g.) were heated under reflux in acetone (100 c.c.), and gave the triacetate of 2 : 3-dimercaptopropanol (1·9 g.), b. p. 120°/0·05 mm., n_D^{23} 1·5105 (Evans and Owen, *loc. cit.*, found n_D^{20} 1·5140); on acid hydrolysis, 2 : 3-dimercaptopropanol was obtained, b. p. 81°/1 mm., n_D^{21} 1·5710 (Found : thiol S, 49·8. Calc. for $C_3H_8OS_2$: S, 51·6%).

Non-interaction of Potassium Thiolacetate and 3-*Toluene*-p-*sulphonyl* 1 : 2-5 : 6-*Di*iso*propylidene Glucose.*—The toluene-*p*-sulphonate (1 g.), potassium thiolacetate (0·55 g.), and acetone (50 c.c.) were heated at 110° in a sealed tube for 18 hours. Unchanged toluene-*p*-sulphonate (0·9 g.) was recovered, m. p. and mixed m. p. 120°, after recrystallisation from acetone.

Action of Potassium Thiolacetate on 5 : 6-*Ditoluene*-p-*sulphonyl* 1 : 3-2 : 4-*Diethylidene Sorbitol.*—The ditoluene-*p*-sulphonate (5 g.) and potassium thiolacetate (4·5 g.) in acetone (100 c.c.) were heated under reflux for 6 hours. On addition of water to the filtered and concentrated solution, a solid (3·5 g.; m. p. 125°) was deposited. Recrystallisation from methanol gave needles of 5-*toluene*-p-*sulphonyl* 6-*acetyl* 1 : 3-2 : 4-*diethylidene* 6-*thiosorbitol*, m. p. 128°, $[\alpha]_D^{21}$ −23·2° (*c*, 2 in chloroform) (Found : C, 50·9; H, 5·6. $C_{19}H_{26}O_8S_2$ requires C, 51·1; H, 5·85%). Light absorption : max. 2260 A., ε 21,000. This compound (1 g.) was recovered unchanged, m. p. and mixed m. p. 128°, after being heated with potassium thiolacetate (0·5 g.) in acetone (25 c.c.) at 110° for 15 hours.

Action of Potassium Thiolacetate on 5 : 6-*Dimethanesulphonyl* 1 : 3-2 : 4-*Diethylidene Sorbitol.*—The dimethanesulphonate (1 g.) and potassium thiolacetate (1·2 g.) in acetone (25 c.c.) were heated under reflux for 6 hours. Only 0·05 g. of a dark water-insoluble product was obtained. With a shorter time of reaction (1 hour) a dark oil (0·7 g.) was isolated, but it appeared to contain much unchanged starting material.

Non-interaction of Potassium Thiolacetate and Phenyl Toluene-p-*sulphonate.*—The toluene-*p*-

sulphonate (1 g.), potassium thiolacetate (0·9 g.), and acetone (50 c.c.) were heated at 110° for 18 hours. Unchanged starting material (0·9 g.) was obtained, having m. p. 93°, raised to 95° on recrystallisation from ethanol.

*Action of Potassium Thiolacetate on the Isomeric Toluene-*p*-sulphonate–Benzoates of Propane-*1 : 2-*diol.*—(i) The material of m. p. 79° (5 g.) and potassium thiolacetate (3·5 g.) in acetone (50 c.c.) were heated under reflux for 1 hour; a quantity of potassium toluene-*p*-sulphonate was formed during this time. The cooled mixture was filtered, and the filtrate was concentrated to 10 c.c. and diluted with water, whereupon a semi-solid product was precipitated. This was collected, and on recrystallisation from methanol it gave the 2-toluene-*p*-sulphonate 1-benzoate of propane-1 : 2-diol, identical (m. p. and mixed m. p. 105°) with that described above. Evaporation of the mother-liquors from the crystallisation gave an oil, which on distillation furnished 2-*benzoyloxypropyl* 1-*thiolacetate* (1·2 g.), b. p. 122°/1 mm., n_D^{20} 1·5328 (Found: C, 60·8; H, 6·2. $C_{12}H_{14}O_3S$ requires C, 60·45; H, 5·9%); a small non-volatile residue consisted mainly of the compound, m. p. 105°. Treatment of the thiolacetate (0·1 g.) in ethanol (10 c.c.) with 1-chloro-2 : 4-dinitrobenzene (0·085 g., 1 mol.) and 10% aqueous sodium hydroxide (0·35 c.c., 2 mol.) under reflux for 10 minutes, followed by dilution with water, gave a precipitate of 2 : 4-*dinitrophenyl* 2-*benzoyloxypropyl sulphide*, which formed yellow needles (0·1 g.), m. p. 139°, from ethanol (Found: N, 7·75. $C_{16}H_{14}O_6N_2S$ requires N, 7·75%); the same product was obtained when the amount of sodium hydroxide was increased to 3 mols., indicating the resistance of the secondary benzoyl group towards hydrolysis under these conditions (compare the primary isomer, below).

(ii) The compound, m. p. 105° (3 g.), was recovered unchanged (2·9 g.) after being heated with potassium thiolacetate (2·1 g.) and acetone (50 c.c.) under reflux for 1 hour. The same mixture was therefore heated in a sealed tube at 110° for 15 hours, and gave 1-*benzoyloxypropyl* 2-*thiolacetate* (1·2 g.), b. p. 118°/1 mm., n_D^{20} 1·5248 (Found: C, 60·8; H, 6·05. $C_{12}H_{14}O_3S$ requires C, 60·45; H, 5·9%). When this compound (0·1 g.) was heated under reflux for 10 minutes in ethanol (10 c.c.) with 1-chloro-2 : 4-dinitrobenzene (0·085 g.) and 10% aqueous sodium hydroxide (0·53 c.c., 3 mols.), the subsequent addition of water gave 2 : 4-*dinitrophenyl* 2-*hydroxy*iso*propyl sulphide*, which crystallised from aqueous ethanol as pale yellow needles, m. p. 87° (Found: N, 10·9. $C_9H_{10}O_5N_2S$ requires N, 10·85%).

Light-absorption data were kindly determined by Dr. E. A. Braude.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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111. *Dithiols. Part V. Further Non-vicinal Dithiols.*

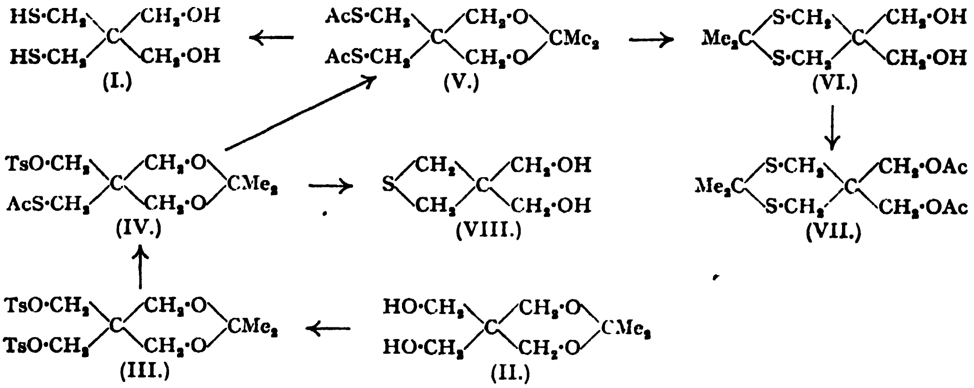
By PETER BLADON and L. N. OWEN.

The sulphonyloxy–thiolacetate exchange reaction (Chapman and Owen, preceding paper) has been applied to the preparation of dithiopentaerythritol, 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (*dithio*iso*mannide*), and 1 : 6-*dithiomannitol*. Two unexpected instances of the fission of an *iso*propylidene group have been encountered in some derivatives of pentaerythritol. The formation of a cyclic sulphide, by removal of the toluene-*p*-sulphonyl group from a 1-tosyl-3-acetylthio-compound, is recorded.

DITHIOPENTAERYTHRITOL (I) was first prepared by Backer and Tamsma (*Rec. Trav. chim.*, 1938, **57**, 1183) by interaction of pentaerythritol dibromohydrin with sodium disulphide, followed by reduction of the intermediate cyclic disulphide with sodium in liquid ammonia. Peppel and Signaigo (U.S.P. 2,402,665) used a similar method, but reduced the disulphide by hydrogenation under pressure over a cobalt polysulphide catalyst.

It was thought that a more convenient laboratory method for the preparation of (I) could be based on the sulphonyloxy–thiolacetate exchange reaction described by Chapman and Owen (Part IV; preceding paper), since suitable starting materials are readily obtained by protection of two of the hydroxyl groups in pentaerythritol by the formation of cyclic acetals, either with aldehydes (Read, *J.*, 1912, **101**, 2090; Schulz and Tollens, *Annalen*, 1896, **289**, 28; Skrabal and Kalpasanoff, *Ber.*, 1928, **61**, 55; Böeseken and Felix, *Ber.*, 1928, **61**, 787; Fairbourne and Woodley, *J.*, 1926, 3240) or with ketones (Böeseken, *Rec. Trav. chim.*, 1922, **41**, 722; Skrabal and Zlatewa, *Z. physikal. Chem.*, 1926, **119**, 305; Böeseken and Hermans, *Ber.*, 1922, **55**, 3760; Böeseken and Felix, *Ber.*, 1929, **62**, 1310; Orthner, *Ber.*, 1928, **61**, 116). It is necessary to remove the protecting groups at a later stage in the synthesis, and since the cyclic acetals with ketones appear to be more readily hydrolysed than those with aldehydes (Skrabal and Zlatewa, *loc. cit.*), the *iso*propylidene derivative (II) was chosen, and was prepared by a modification of Orthner's method (*loc. cit.*).

Treatment of (II) with two moles of toluene-*p*-sulphonyl chloride in pyridine afforded *ditosyl* iso*propylidene pentaerythritol* (III). Similarly, with methanesulphonyl chloride in pyridine, *dimethanesulphonyl* iso*propylidene pentaerythritol* was formed. Throughout this work, Tipson's general method (*J. Org. Chem.*, 1944, **9**, 235) has been followed for the preparation of tosyl and methanesulphonyl compounds; he pointed out that it is essential in many cases to keep the temperature of the reaction mixture below 5°, and in this connection it is of interest that Rapoport (*J. Amer. Chem. Soc.*, 1946, **68**, 341; U.S.P. 2,441,595) found that monoiso-



(Ts = p-$C_6H_4Me{\cdot}SO_2{\cdot}$.)

propylidene pentaerythritol with toluene-*p*-sulphonyl chloride in warm pyridine gave the corresponding dichloro-compound instead of the ditoluene-*p*-sulphonate.

When the ditosyl compound was refluxed with potassium thiolacetate in acetone for a limited time, only one of the tosyloxy-groups was replaced, and O-*tosyl* S-*acetyl* OO-iso*propylidene monothiopentaerythritol* (IV) was obtained. Prolonged treatment of this product with potassium thiolacetate and acetone gave *di*-S-*acetyl* OO-iso*propylidene dithiopentaerythritol* (V). The same compound was obtained by reaction of the dimethanesulphonate with potassium thiolacetate in boiling ethanol.

An attempt was made to remove simultaneously the acetyl and *iso*propylidene residues in (V) by hydrolysis with hot aqueous methanolic hydrogen chloride. The main product, which separated from the reaction mixture, was a high-melting solid containing no free thiol; furthermore, it showed no selective light absorption in the ultra-violet and was therefore not a thiolacetate. It was identified as *SS-iso*propylidene dithiopentaerythritol (VI), previously prepared by Backer and Tamsma (*loc. cit.*). Evaporation of the mother-liquors gave some dithiopentaerythritol (I). The *iso*propylidene compound (VI) may be formed either by reaction of the dithiol with acetone liberated during the hydrolysis, or by hydrolysis of the acetyl groups in (V), followed by direct migration of the acetone residue (possibly through an intermediate *OS-iso*propylidene compound). The mechanism of this reaction will be investigated further, but it may be pointed out that the migration of *iso*propylidene residues in certain dulcitol derivatives, catalysed by quinoline hydrochloride, has been observed by Hann, Maclay, and Hudson (*J. Amer. Chem. Soc.*, 1939, **61**, 2432). In accordance with the known stability of the cyclic acetals of dithiols, (VI) was unaffected by acid hydrolysis.

When the bisacetylthio-compound (V) was hydrolysed with methanolic potassium hydroxide, it gave a small yield of *SS-iso*propylidene dithiopentaerythritol (VI), identical with the material obtained by acid hydrolysis. This result was quite unexpected, since *iso*propylidene residues are normally unaffected by alkali.

*SS-iso*Propylidene dithiopentaerythritol (VI) was characterised by acetylation to yield *di*-O-*acetyl* SS-iso*propylidene dithiopentaerythritol* (VII), isomeric with (V), and by reaction with methanesulphonyl chloride in pyridine to yield *di*-O-*methanesulphonyl* SS-iso*propylidene dithiopentaerythritol*, both derivatives being crystalline. Acetylation of dithiopentaerythritol gave a liquid *tetra-acetate.*

Treatment of tosyl *S*-acetyl *iso*propylidene monothiopentaerythritol (IV) with sodium methoxide in methanol–chloroform (the usual conditions for the formation of anhydro-compounds in the carbohydrate field; cf. Peat and Wiggins, *J.*, 1938, 1088) resulted in elimination of sodium toluene-*p*-sulphonate and of the *iso*propylidene residue, with formation of a small amount of 3 : 3-*bishydroxymethylthietan* (VIII). The reaction thus provided another example of the unexpected loss of an *iso*propylidene group; as far as we are aware, it is also the first occasion on which a cyclic sulphide has been prepared by such a method.

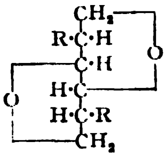
During the general investigation of the sulphonyloxy–thiolacetate exchange reaction (Part IV; *loc. cit.*) it was found that secondary groups differed considerably amongst themselves in their reactivity. Since, however, it had been shown by Hockett, Fletcher, Sheffield, Goepp, and Soltzberg (*J. Amer. Chem. Soc.*, 1946, **68**, 930) that the two secondary toluene-*p*-sulphonyloxy-groups in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydromannitol were capable of being replaced by iodine when the compound was treated with sodium iodide in acetone at 120°, it appeared probable that an interchange with potassium thiolacetate could be effected; the compound actually used was the 2 : 5-dimethanesulphonate (IX) (Montgomery and Wiggins, *J.*, 1948, 2204), which reacted with potassium thiolacetate in ethanol at 110° to give solid *diacetyl* 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (X), together with much uncrystallisable material. Some deacetylation appeared to occur during the reaction, and the crude product was therefore re-acetylated before being worked up. The thiolacetate (X) was smoothly deacetylated by heating with methanolic hydrogen chloride, and gave 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (XI) as a low-melting solid; it was characterised as the *bis*-2 : 4-*dinitrophenyl* derivative (XII), which showed a remarkably high optical rotation in nitrobenzene solution ($[\alpha]_D^{19}$ −398°).

A second possible route to dithio*iso*mannide was explored. This was based on an observation by Freudenberg and Wolf (*Ber.*, 1927, **60**, 232), who found that the 3-methyl xanthate of di*iso*propylidene glucose, when heated to 300°, underwent a rearrangement and gave a dithiolcarbonate, from which 3-thioglucose was obtained by hydrolysis:

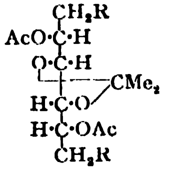
$$\text{R·O·CS·SMe} \longrightarrow \text{R·S·CO·SMe} \longrightarrow \text{R·SH (R = di}\textit{iso}\text{propylidene glucose residue)}$$

Treatment of 1 : 4-3 : 6-dianhydromannitol with sodium in liquid ammonia gave the disodium derivative which, by the action of carbon disulphide, followed by methyl iodide, was converted into the 2 : 5-*di*(*methyl xanthate*) of *iso*mannide (XIII). This, however, failed to undergo any rearrangement on distillation at 170°, since a portion of the product, on hydrolysis, gave *iso*mannide; when it was heated at 290°, extensive decomposition occurred, but the distillate still appeared to consist mainly of unchanged xanthate.

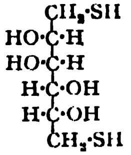
In Part III (Evans, Fraser, and Owen, *J.*, 1949, 248) the preparation of 1 : 6-dithiomannitol was described. Since this compound exhibited some unusual physiological effects, its synthesis by an application of the sulphonyloxy–thiolacetate exchange reaction was devised as a possibly more convenient route. The starting material was 1 : 6-ditosyl 2 : 5-diacetyl 3 : 4-*iso*propylidene mannitol (XIV) (Wiggins, *J.*, 1946, 386). On treatment with potassium thiolacetate in boiling acetone this gave 1 : 2-5 : 6-*tetra-acetyl* 3 : 4-iso*propylidene* 1 : 6-*dithiomannitol* (XV). Removal of the acetyl and *iso*propylidene groups by acid hydrolysis then gave a crude dithiol, which when purified by acetylation afforded crystalline *hexa-acetyl* 1 : 6-*dithiomannitol*. This compound, however, was not identical with the hexa-acetate described by Evans, Fraser, and Owen (*loc. cit.*); furthermore, on deacetylation with methanolic hydrogen chloride it gave pure 1 : 6-*dithiomannitol* (XVI), which differed from the dithiol previously described under this name. This discrepancy led to a reinvestigation of the " dithiomannitol " prepared by the earlier route, and has resulted in the discovery that the original dithiol, its hexa-acetate, and the 1 : 6-dibromide from which it was derived, have the dulcitol configuration (see Bladon, Owen, Overend, and Wiggins, *Nature*, 1949, **164**, 567).



(IX; R = O·SO$_2$·Me.)
(X; R = SAc.)
(XI; R = SH.)
[XII; R = S·C$_6$H$_3$(NO$_2$)$_2$.]
(XIII; R = O·CS·SMe.)



(XIV; R = OTs.)
(XV; R = SAc.)



(XVI.)

EXPERIMENTAL.

(Light-absorption measurements, in ethanol, were kindly determined by Dr. E. A. Braude.)

iso*Propylidene Derivatives of Pentaerythritol*.—Finely powdered pentaerythritol (180 g.) was stirred vigorously with a mixture of acetone (2 l.), water (670 c.c.), and concentrated hydrochloric acid (80 c.c.) for 15 hours. Unchanged pentaerythritol (81·5 g.) was filtered off and washed with acetone. The filtrate was stirred with potassium carbonate (500 g.), added in small portions, and the lower, aqueous layer was removed and extracted once with ether–acetone (1 : 1; 500 c.c.). The combined acetone–ether solution was dried by stirring with potassium carbonate (500 g.) for ½ hour, and was then filtered and evaporated. The residue (74 g.), after being dried by distillation with benzene and alcohol under reduced pressure, was powdered and extracted (Soxhlet) with light petroleum (b. p. 40—60°) for ½ hour. Evaporation of this extract gave crude di*iso*propylidene pentaerythritol (4·4 g.), b. p. 160—170° (bath)/30 mm., m. p. 105—111°. The mono*iso*propylidene derivative (58·3 g.) was obtained by exhaustive extraction of the residue with ether in the same apparatus (24 hours); the m. p., 120—125°, was not changed by recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°). A residue (5·1 g.), m. p. >150°, probably unchanged pentaerythritol, remained after the ether extraction.

For the mono- and di-*iso*propylidene derivatives, respectively, Orthner (*loc. cit.*) gives m. p. 128—129° and 117—117·5°; Skrabal and Kalpasanoff (*loc. cit.*) give 135° and 116°; Rapoport (*loc. cit.*) gives 126—127° for the mono-compound.

Ditosyl iso*Propylidene Pentaerythritol* (III).—The mono*iso*propylidene compound (17·6 g.) in dry pyridine (150 c.c.) was treated with toluene-*p*-sulphonyl chloride (42 g., 10% excess), the temperature being kept below 5°. After 12 hours at 0°, water (700 c.c.) was slowly added, and the precipitated solid (m. p. 140—146°) was collected and washed with water. Recrystallisation from acetone gave colourless needles (34·6 g., 71%) of *ditosyl* iso*propylidene pentaerythritol*, m. p. 152—153° (Found: C, 54·4; H, 5·9; S, 13·2. $C_{22}H_{28}O_8S_2$ requires C, 54·2; H, 5·8; S, 13·2%).

Dimethanesulphonyl iso*Propylidene Pentaerythritol*.—The mono*iso*propylidene compound (17·6 g.) was added in small portions to a cooled solution of methanesulphonyl chloride (25·2 g., 10% excess) in dry pyridine (100 c.c.), the temperature being kept below 10°. After being kept overnight at 0°, the mixture was poured into water (400 c.c.). The brown solid was collected, washed with water, and recrystallised from methanol to give *dimethanesulphonyl* iso*propylidene pentaerythritol* (17·9 g.), m. p. 107—110°, raised on further recrystallisation to 110—112° (Found: C, 35·9; H, 6·5; S, 19·35. $C_{10}H_{20}O_8S_2$ requires C, 36·1; H, 6·1; S, 19·3%).

Reaction of Ditosyl iso*Propylidene Pentaerythritol with Potassium Thiolacetate*.—The ditosyl compound (34·5 g., 0·0895 mol.), potassium thiolacetate (20·3 g., 0·178 mol.), and pure acetone (180 c.c.) were heated under reflux for 8 hours, a further quantity of potassium thiolacetate (4 g., 0·035 mol.) being added after 6 hours. The reaction mixture was cooled and filtered, and the salts were well washed with acetone. The filtrate was evaporated, and the residue was treated with water (50 c.c.) and extracted thrice with chloroform (50 c.c. portions). Evaporation of the dried (Na_2SO_4) extracts gave a residue (26·5 g.) which was dissolved in methanol and kept overnight at 0°. The solid (18·7 g.; m. p. 85—92°) was collected and recrystallised from methanol to give O-*tosyl* S-*acetyl* OO-iso*propylidene monothiopentaerythritol* (IV), m. p. 91—93° (Found: C, 52·85; H, 6·4; S, 16·3. $C_{17}H_{24}O_6S_2$ requires C, 52·55; H, 6·2; S, 16·5%). The compound was unstable and underwent extensive decomposition after storage for a few months. Concentration of the methanolic mother-liquors gave further crops of solid, m. p. 55—60°, which probably contained the bisthiolacetate (see below).

Reaction of Tosyl S-*Acetyl* OO-iso*Propylidene Monothiopentaerythritol with Potassium Thiolacetate*.—The above monotosyl compound (7·76 g.), potassium thiolacetate (6·8 g., large excess), and acetone (70 c.c.) were heated under reflux for 30 hours. The precipitated solid was filtered off and well washed with acetone. The filtrates were evaporated to small bulk, the residue was treated with water, and the oil was isolated by chloroform extraction followed by evaporation of the dried (Na_2SO_4) extracts. Crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) failed to give any pure material; apparently the bisthiolacetate and the monotosyl-monothiolacetate form a mixture, m. p. 57—59°, which is not readily separable by crystallisation. Accordingly, the crude product was distilled, b. p. 120° (bath)/0·0001 mm., and the solid distillate (3·95 g., 67·5%) was recrystallised from methanol. *Di*-S-*acetyl* OO-iso*propylidene dithiopentaerythritol* (V) formed colourless tablets, m. p. 63—65° (Found: C, 49·7; H, 7·3; S, 22·15. $C_{12}H_{20}O_4S_2$ requires C, 49·3; H, 6·9; S, 21·9%). Light absorption: max. 2290 A., ε 8500.

Reaction of Dimethanesulphonyl iso*Propylidene Pentaerythritol with Potassium Thiolacetate*.—The dimethanesulphonate (17·85 g., 0·054 mol.), potassium thiolacetate (18·5 g., 0·161 mol.), and ethanol (170 c.c.) were heated under reflux for 13 hours. The potassium methanesulphonate (15 g.) was removed and washed with ethanol. The filtrates were concentrated under reduced pressure, then diluted with water and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a syrup (14·9 g., 95%) which crystallised on being stirred with methanol. Recrystallisation from this solvent gave large rectangular tablets of di-*S*-acetyl *OO*-*iso*propylidene dithiopentaerythritol (12·0 g., 76%), m. p. 63—65°, undepressed on admixture with the material prepared from the tosyl compound.

Acid Hydrolysis of Di-S-*acetyl* OO-iso*Propylidene Dithiopentaerythritol*.—The compound (10 g.) was heated under reflux for 2 hours with methanol (20 c.c.) and 2N-aqueous hydrochloric acid (20 c.c.) in an atmosphere of nitrogen. Concentration of the solution then gave a solid (4·4 g.), which was collected, washed with water, and recrystallised from dioxan. *SS*-*iso*Propylidene dithiopentaerythritol (VI) formed flattened needles, m. p. 198—200°, which did not show selective ultra-violet-light absorption or give a thiol reaction (Found: S, 30·7. Calc. for $C_8H_{16}O_2S_2$: S, 30·8%). Backer and Tamsma (*loc. cit.*) give m. p. 199·5—200·5°. Further concentration of the original aqueous solution gave a second crop of crystals (1 g.), m. p. 95—97°, and, on complete evaporation, a final residue (1 g.), m. p. 87—89°. Recrystallisation of these from benzene gave plates, m. p. 95—96°, of dithiopentaerythritol (I) (Found: thiol S, 37·9. Calc. for $C_5H_{12}O_2S_2$: S, 38·1%). Acetylation of dithiopentaerythritol with acetic anhydride and sodium acetate at 100° for 8 hours gave the *tetra-acetate* as a colourless oil, b. p. 100—120° (bath)/0·0001 mm., n_D^{15} 1·5092 (Found: C, 46·55; H, 6·2; S, 19·15. $C_{13}H_{20}O_6S_2$ requires C, 46·5; H, 6·0; S, 19·1%). Light absorption: max. 2310 A., ε 8400.

Alkaline Hydrolysis of Di-S-*acetyl* OO-iso*Propylidene Dithiopentaerythritol*.—The compound (0·93 g.) was kept overnight under nitrogen with potassium hydroxide (1·5 g.) in methanol (15 c.c.). The alkali was then neutralised with carbon dioxide, water added, and the mixture extracted thrice with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a pale yellow oil (0·65 g.) containing free thiol, which on distillation furnished a liquid forerun, b. p. 90—120° (bath)/0·0001 mm., and a semi-solid material

(0·26 g.), b. p. 120—150° (bath)/0·0001 mm. The latter on crystallisation from methanol gave *SS-iso*propylidene dithiopentaerythritol, m. p. and mixed m. p. 197—199°.

*SS-iso*Propylidene dithiopentaerythritol was recovered largely unchanged (64%) after being heated with dioxan–5N-hydrochloric acid (1 : 1) for 4 hours on the steam-bath, followed by dilution with water; the aqueous filtrate gave only a faintly positive thiol test with nitroprusside and alkali.

The *diacetate* (VII), m. p. 71—72° after recrystallisation from methanol, was prepared by heating the compound with acetic anhydride and sodium acetate on the steam-bath for 6 hours (Found : C, 49·6; H, 7·0; S, 21·85. $C_{12}H_{20}O_4S_2$ requires C, 49·3; H, 6·9; S, 21·9%).

The *dimethanesulphonate* was prepared by treatment of *SS-iso*propylidene dithiopentaerythritol with a slight excess of methanesulphonyl chloride in pyridine for 12 hours at 0°; it formed fine needles, m. p. 123—125°, from acetone–methanol (Found : C, 33·2; H, 5·6; S, 35·2. $C_{10}H_{20}O_6S_4$ requires C, 32·9; H, 5·5; S, 35·2%).

Reaction of Tosyl S-*Acetyl* OO-iso*Propylidene Monothiopentaerythritol with Sodium Methoxide*.—The tosyl compound (1·94 g.) in chloroform (5 c.c.) was treated at 0° with sodium (0·14 g.) in dry methanol (3 c.c.). Sodium toluene-*p*-sulphonate rapidly separated, at first as a gel, and subsequently in crystalline form. The mixture was kept for an hour at room temperature, and at 0° overnight. Water (15 c.c.) was then added, and the chloroform layer was separated; the aqueous solution was extracted thrice more with chloroform. The dried (Na_2SO_4) extracts were evaporated and the residue was brought to crystallisation by evaporation several times with light petroleum (b. p. 40—60°). Crystallisation from methanol gave a small amount (0·19 g.) of ditosyl *iso*propylidene pentaerythritol, m. p. and mixed m. p. 152—154°, presumably present as impurity in the starting material. The mother-liquors were evaporated, and the residue was heated under reduced pressure; 3 : *3-bishydroxymethylthietan* (VIII) (54 mg.), m. p. 72—74°, sublimed at 90—120° (bath temp.)/0·01 mm. (Found : C, 44·8; H, 7·5; S, 24·1. $C_5H_{10}O_2S$ requires C, 44·8; H, 7·5; S, 23·9%). A considerable amount of viscid non-volatile material probably consisted of polymer.

1 : 4-3 : 6-*Dianhydromannitol* (cf. Hockett *et al.*, *loc. cit.*; Montgomery and Wiggins, *J.*, 1947, 433).—Mannitol (50 g.) and toluene-*p*-sulphonic acid (5 g.) were thoroughly mixed by shaking in a 400-c.c. Claisen flask, fitted with the usual capillary leak and thermometer, and connected to a cooled receiver. The pressure was reduced to 50 mm., and the mixture was heated to 160—180° till molten. The bath temperature was then reduced to 140—150° and kept thereat for 1 hour whilst water was collected in the receiver. The pressure was then reduced to 2 mm., and as much material as possible was distilled into a clean receiver at a bath temperature of 160—200°, care being taken, particularly towards the end of the distillation, to keep the frothing under control. The pale yellow distillate, b. p. 120—130°/2 mm. (12·9 g.), crystallised on being seeded with *iso*mannide, and after recrystallisation from the minimum amount of ethyl acetate it formed prisms (10·5 g., 26%), m. p. 85—86°. The preparation was successfully carried out on twice this scale.

Diacetyl 2 : 5-*Dithio*-1 : 4-3 : 6-*dianhydromannitol* (X).—2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (Montgomery and Wiggins, *J.*, 1948, 2204) (6·0 g.), potassium thiolacetate (6·9 g.; excess), and thiolacetic acid (0·2 c.c.) in ethanol (30 c.c.) were heated in a sealed tube at 110—115° for 12 hours. The precipitated potassium methanesulphonate (5·5 g.; calc., 5·4 g.) was removed, and the alcoholic filtrates were evaporated to dryness. The residue was acetylated by heating with acetic anhydride (20 c.c.) and fused sodium acetate (2 g.) for 2 hours on the steam-bath, in order to counteract any deacetylation which might have occurred during the initial reaction. The resulting mixture was stirred with water to decompose the excess of acetic anhydride, and the oil was isolated by 4 extractions with chloroform (35 c.c.; 3 × 15 c.c.). The extracts were washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to a red oil (6·3 g.) which was fractionally distilled in nitrogen. After removal of some low-boiling material, the main product was collected at 135—140°/0·1 mm. (bath temp. 190—200°), n_D^{17} 1·558—1·552; on storage, it solidified. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave prisms, m. p. 35—37°; yield 3·25 g. (62%). Further recrystallisation from the same solvents gave colourless crystals, m. p. 36—37·5°, $[\alpha]_D^{17}$ +19·2° (*c*, 2·2 in chloroform), of *diacetyl* 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* (Found : C, 46·1; H, 5·65; S, 24·55. $C_{10}H_{14}O_4S_2$ requires C, 45·8; H, 5·4; S, 24·45%). Light absorption : max. 2310 A., ε 8400.

2 : 5-*Dithio*-1 : 4-3 : 6-*dianhydromannitol* (XI).—The above diacetyl compound (3·12 g.) was heated under reflux with 2·5% hydrogen chloride in methanol (50 c.c.) for 4 hours. The solvent was removed by distillation under reduced pressure and the residual oil (2·12 g., 100%) was kept under reduced pressure over potassium hydroxide, whereupon it partly solidified. Distillation furnished 2 : 5-*dithio*-1 : 4-3 : 6-*dianhydromannitol* as a pale yellow oil, m. p. 15—16°, b. p. 60—80° (bath)/0·0001 mm., n_D^{17} 1·5692, $[\alpha]_D^{18}$ +85° (*c*, 2·5 in chloroform), $[\alpha]_D^{19}$ +120° (*c*, 1·4 in 0·2N-aqueous sodium hydroxide) (Found : C, 40·6; H, 5·75; S, 36·1; thiol S, 36·4. $C_6H_{10}O_2S_2$ requires C, 40·4; H, 5·65; S, 36·0%). The dithiol was readily soluble in all the common organic solvents.

Bis-2 : 4-*dinitrophenyl Derivative* (XII).—The dithiol (0·26 g.) was heated under reflux with 2 : 4-dinitrochlorobenzene (0·6 g.) and potassium hydroxide (0·17 g.) in ethanol (10 c.c.) for 1 hour. A copious precipitate of potassium chloride was produced. On pouring the solution into water, an emulsion was obtained, but this was broken on acidification with dilute sulphuric acid. The brown precipitate was collected, washed with water, and dried; yield, 0·73 g. (98%); m. p. 145—150°. One recrystallisation from aqueous acetic acid, and three from acetone gave the *derivative* as yellow needles, m. p. 187—188°, $[\alpha]_D^{19}$ −398° (*c*, 1 in nitrobenzene) (Found : C, 41·9; H, 3·0; N, 11·1. $C_{18}H_{14}O_{10}N_4S_2$ requires C, 42·35; H, 2·8; N, 11·0%). The substance was difficultly soluble in most common solvents, but dissolved readily in hot acetic acid or acetone.

1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di*(*methyl Xanthate*) (XIII).—1 : 4-3 : 6-Dianhydromannitol (7·3 g.) in liquid ammonia (300 c.c.) was treated with finely divided sodium (2·3 g.). After a few minutes, during which the blue colour had not entirely disappeared, the ammonia was allowed to evaporate, and the last traces were removed from the residue by heating under reduced pressure on the steam-bath. The fine white powder was heated under reflux with carbon disulphide (80 c.c.) for 22 hours. Methyl iodide (43 g.) was then added, and the heating continued for a further 16 hours. The mixture was

shaken with water (100 c.c.), and the lower aqueous layer was separated and extracted thrice with ether (100-c.c. portions). The combined carbon disulphide and ethereal solutions were dried (Na_2SO_4) and evaporated. The deep-red residue (12·2 g.) on distillation from a wide-necked retort under high vacuum gave some very volatile material (possibly dimethyl *iso*mannide) which condensed in the liquid-air trap. The second fraction (0·43 g.), b. p. <120° (bath)/0·0001 mm., n_D^{26} 1·6387, $[\alpha]_D^{21}$ +159° (*c*, 2·3 in chloroform), probably consisted mainly of monomethyl *iso*mannide mono(methyl xanthate). After the collection of some intermediate fractions (2·8 g.), the main bulk (6·2 g.) distilled at 170° (bath)/0·0001 mm. Redistillation gave the *di*(*methyl xanthate*) as a viscous orange liquid, n_D^{20} 1·6318, $[\alpha]_D^{21}$ +266° (*c*, 2·8 in chloroform) (Found : C, 36·6; H, 4·5; S, 39·3. $C_{10}H_{14}O_4S_4$ requires C, 36·8; H, 4·3; S, 39·3%). Light absorption : max. 2280, 2800 A.; ε 10,100 and 14,000, respectively. After being kept for several weeks, the syrup crystallised. Two recrystallisations from ethyl acetate–methanol afforded pale yellow plates, m. p. 58—60°, $[\alpha]_D^{18}$ +274° (*c*, 2·0 in chloroform) (Found : C, 37·0; H, 4·5; S, 39·3%). Light absorption : max. 2270, 2800 A.; ε 14,500 and 17,500; infl. 2730 A.; ε 15,000.

Reaction of 1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di*(*methyl Xanthate*) *with Sodium Methoxide*.—The above compound (1 g.; a syrup) was heated under reflux for 4 hours with sodium methoxide (1 g.) in methanol (15 c.c.). The alkali was then neutralised with carbon dioxide, the solution was filtered, and the filtrate and washings were evaporated to dryness. The crystalline residue was extracted overnight in a Soxhlet apparatus with chloroform; evaporation of these extracts gave *iso*mannide (0·43 g.), which was characterised by conversion into the dimethanesulphonyl derivative, m. p. and mixed m. p. 101—102°, $[\alpha]_D^{19}$ +134° (*c*, 1 in chloroform).

Pyrolysis of 1 : 4-3 : 6-*Dianhydromannitol* 2 : 5-*Di*(*methyl Xanthate*).—A portion of the syrup (1·2 g.) was heated at 290° at atmospheric pressure in a small retort held vertically in a metal-bath. Under these conditions, the compound refluxed gently, and slowly evolved a small amount of volatile material which collected in a liquid-air trap attached to the end of the retort. The temperature was allowed to fall to 250° during one hour, and the retort was then rearranged for distillation in the usual way. A small quantity (0·06 g.) of an oil was collected at 120—125° (bath)/0·0001 mm., which probably consisted of unchanged xanthate; light absorption : max. 2260, 2810 A., $E_{1\,cm.}^{1\%}$ 240, 220; infl. 2870 A., $E_{1\,cm.}^{1\%}$ 160. A considerable amount of dark viscous material remained in the retort.

1 : 2-5 : 6-*Tetra-acetyl* 3 : 4-iso*Propylidene* 1 : 6-*Dithiomannitol* (XV).—1 : 6-Ditosyl 2 : 5-diacetyl 3 : 4-*iso*propylidene mannitol, m. p. 111—113°, $[\alpha]_D^{20}$ +22·9° (*c*, 1·7 in chloroform) was prepared by Wiggins's method (*J.*, 1946, 384). This substance (8 g.), potassium thiolacetate (4·5 g.), and dry acetone (30 c.c.) were heated under reflux for 4 hours. Precipitated potassium toluene-*p*-sulphonate was removed (6·7 g., 102%) and washed with acetone, and the filtrates were concentrated and then diluted with water (30 c.c.). The oily layer was taken up in chloroform, and the aqueous portion was extracted thrice with chloroform. Removal of solvent from the dried (Na_2SO_4) extracts gave the *tetra-acetyl* derivative as a dark viscid oil, which could be distilled only in small quantities, b. p. 120° (bath)/0·0001 mm., n_D^{18} 1·4950, $[\alpha]_D^{20}$ +114° (*c*, 1·4 in chloroform) (Found : C, 47·6; H, 6·4; S, 14·9. $C_{17}H_{26}O_8S_2$ requires C, 48·35; H, 6·2; S, 15·2%). Light absorption : max. 2280 A., ε 8000.

1 : 6-*Dithiomannitol* (XVI).—The above bisthiolacetate (5·6 g.; not distilled) was heated under reflux for 8 hours with 2% methanolic hydrogen chloride in an atmosphere of nitrogen. The solvent was then removed under reduced pressure, but the residual glass could not be induced to crystallise, and possibly contained some partly hydrolysed material. It was therefore heated for a further 8 hours with 2N-hydrochloric acid (7 c.c.) at 100°, under nitrogen. Freeze-drying of the solution at *ca.* 0° under reduced pressure then gave the crude dithiol (2·7 g.) as a powder, m. p. 120—135°, $[\alpha]_D^{18}$ +18° (*c*, 1·2 in water) (Found : thiol S, 24·4. $C_6H_{14}O_4S_2$ requires S, 29·9%), which was acetylated by being heated on the steam-bath for 5 hours with acetic anhydride (12 c.c.) and fused sodium acetate (1 g.). The reaction mixture was then stirred with water and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue from methanol gave needles (0·6 g.) of *hexa-acetyl* 1 : 6-*dithiomannitol*, m. p. 107—109°, $[\alpha]_D^{17}$ +81·8° (*c*, 1 in chloroform), raised on further recrystallisation from methanol to m. p. 109—111°, $[\alpha]_D^{18}$ +85° (*c*, 1 in chloroform) (Found : C, 46·5; H, 5·9; S, 13·65. $C_{18}H_{26}O_{10}S_2$ requires C, 46·3; H, 5·6; S, 13·7%). Light absorption : max. 2300 A., ε 8200.

Deacetylation of the hexa-acetate (0·59 g.) by heating under reflux with 2% methanolic hydrogen chloride for 5 hours, followed by evaporation to dryness under reduced pressure, gave a solid (0·3 g.), which was freed from traces of acid by being kept under reduced pressure for several hours over potassium hydroxide. Recrystallisation from methanol gave 1 : 6-*dithiomannitol*, m. p. 155—157°, $[\alpha]_D^{20}$ +1·86° (*c*, 0·6 in water), $[\alpha]_D^{20}$ +15° (*c*, 0·6 in 2·9% aqueous borax) (Found : C, 34·3; H, 6·85; S, 29·4; thiol S, 28·7. $C_6H_{14}O_4S_2$ requires C, 33·6; H, 6·6; S, 29·9%). The dithiol is hygroscopic, and recrystallisation is attended with some difficulty. Unlike 1 : 6-dithiodulcitol (the former " 1 : 6-dithiomannitol "), it is readily soluble in water.

1 : 2-3 : 4-*Diisopropylidene* 1 : 4-*Dithioerythritol*.—In Part III (Evans, Fraser, and Owen, *loc. cit.*) the m. p. of this substance was erroneously given as 145°; it has m. p. 105°.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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112. *Dithiols. Part VI. Ethers of 2 : 3-Dimercaptopropanol with Mannitol and Sorbitol.*

By Peter Bladon and L. N. Owen.

A description is given of experiments directed towards the synthesis of the following water-soluble ethers of " BAL " (2 : 3-dimercaptopropanol) : 1- and 3-(2 : 3-dimercaptopropyl) mannitol; 6-(2 : 3-dimercaptopropyl) sorbitol; and 2-(2 : 3-*dimercaptopropyl*) 1 : 4-3 : 6-*dianhydromannitol*. The *acetyl* derivatives were obtained in each case.

In Part II of this series (Evans and Owen, *J.*, 1949, 244), the preparations of the α- and β-glyceryl ethers of " BAL " (2 : 3-dimercaptopropanol) were described. This work has now been extended to the synthesis of compounds in which the hydroxyl group of " BAL " is etherified by one of the hydroxyl groups of mannitol or sorbitol. The general method was the same as in the earlier work, and involved the preparation of the corresponding fully acetylated allyl ethers. These were made by three general methods :

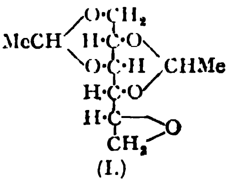
(*a*) Direct allylation of a suitably protected derivative of the hexitol with allyl bromide in the presence of sodium hydroxide. This method has been studied by Yanovsky and his co-workers (*J. Amer. Chem. Soc.*, 1944, **66**, 1625; 1945, **67**, 46), who applied it to the complete allylation of carbohydrates. In the present work, it was necessary to allylate only one of the two hydroxyl groups usually available in the protected hexitols, and the procedure adopted was therefore the addition of allyl bromide to a solution of the hexitol derivative in concentrated aqueous sodium hydroxide.

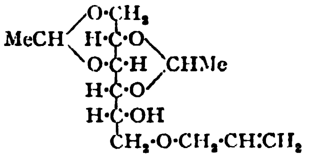
(*b*) Reaction of the sodium derivative of the hydroxy-compound (prepared by treatment with sodium in liquid ammonia) with allyl bromide.

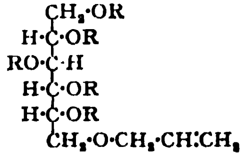
(*c*) Ring-opening of an ethylene oxide anhydro-compound with sodium allyl oxide in allyl alcohol. In the case of terminal epoxides, ring opening proceeds mainly in such a way that the allyloxy-group becomes attached to the terminal carbon atom (cf. the analogous case of ring opening with sodium methoxide, Vargha and Puskás, *Ber.*, 1943, **76**, 859). No Walden inversion occurs, and the product has the configuration of the initial epoxide. With a non-terminal epoxide, the ring opening can occur in two ways, and, since Walden inversion takes place in both cases, neither of the two products has the configuration of the initial epoxide.

The allyl ethers were then subjected to acid hydrolysis to remove the protecting groups (*iso*propylidene or ethylidene), and then fully acetylated, the products being treated with bromine in carbon tetrachloride solution, to yield the dibromopropyl ethers. These compounds, on treatment with potassium thiolacetate in boiling ethanol, gave the corresponding bisthiolacetates. Deacetylation of these was carried out with either barium methoxide or methanolic hydrogen chloride.

The starting material for the preparation of the 6-sorbitol ether of 2 : 3-dimercaptopropanol was 1 : 3-2 : 4-diethylidene sorbitol (Appel, *J.*, 1935, 425; Hockett and Nickerson, *J. Amer. Chem. Soc.*, 1947, **69**, 850). Attempts at the direct allylation of this compound with allyl bromide and alkali, aimed at the formation of a monoallyl derivative, gave mixtures of mono- and di-allyl compounds. Accordingly, the route *via* the anhydro-compound was used. 1 : 3-2 : 4-Diethylidene 5 : 6-anhydrosorbitol (I) was prepared by the method of Vargha and Puskás (*loc. cit.*) (see also Sullivan, *J. Amer. Chem. Soc.*, 1946, **67**, 837; Wiggins, *J.*, 1946, 388). An improved yield (93%) was obtained in the conversion of the intermediate 6-tosyl compound into the anhydro-compound. It was also possible to avoid isolation of the tosyl derivative by treatment of the crude syrup with sodium methoxide, and to isolate the anhydro-compound by sublimation, with little alteration in the overall yield.

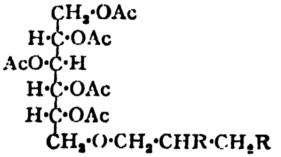

(I.)

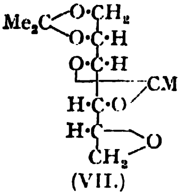

(II.)

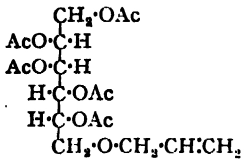

(III; R = H.)
(IV; R = Ac.)

Ring opening of (I) with sodium allyl oxide in allyl alcohol at 100° gave 1 : 3-2 : 4-*diethylidene 6-allyl sorbitol* (II). The crude 6-allyl sorbitol (III) obtained by removal of the ethylidene residues by acid hydrolysis was a syrup, which was acetylated to give *penta-acetyl 6-allyl sorbitol* (IV) as a liquid which could be distilled in a high vacuum.

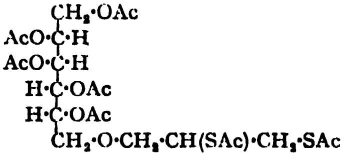
Addition of bromine to this compound gave *penta-acetyl 6-(2 : 3-dibromopropyl) sorbitol* (V), which, on reaction with potassium thiolacetate in boiling ethanol furnished *hepta-acetyl 6-(2 : 3-dimercaptopropyl) sorbitol* (VI). Deacetylation with barium methoxide furnished a crude barium salt of the dithiol, but, as previously found with the barium salt of dimercaptopropylglucoside (cf. Evans and Owen, *J.*, 1949, 244), this could not be purified.

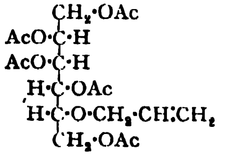

(V; R = Br.)
(VI; R = SAc.)

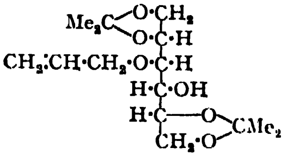

(VII.)


(VIII.)

For the preparation of 2 : 3-dimercaptopropyl 1(or 6)-mannitol ether, 1 : 2-3 : 4-di*iso*propylidene mannitol was used (Wiggins, *J.*, 1946, 13); this was converted into 1 : 2-3 : 4-di*iso*propylidene 5 : 6-anhydromannitol (VII) by a modification of the method of Wiggins (*J.*, 1946, 388), the intermediate 6-tosyl compound not being isolated, but treated directly, in the crude state, with sodium methoxide; the anhydro-compound was then purified by sublimation. Treatment of (VII) with sodium allyl oxide in boiling allyl alcohol gave *6-allyl* 1 : 2-3 : *4-di*iso*propylidene mannitol*, converted by acid hydrolysis into crystalline 1(or 6)-*allyl mannitol*, acetylation of which gave the solid *penta-acetyl* derivative (VIII). With bromine, this gave *penta-acetyl* 1-(2 : 3-*dibromopropyl*) *mannitol* and thence, with potassium thiolacetate, *hepta-acetyl* 1-(2 : 3-*dimercaptopropyl*) *mannitol* (IX) was obtained. Deacetylation with barium methoxide gave a crude barium salt.


(IX.)

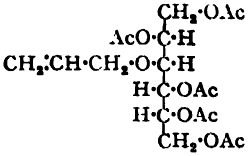

(X.)


(XI.)

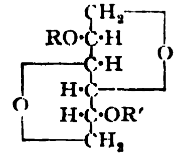
An attempt was made to prepare the above 1-allyl mannitol by direct allylation of 1 : 2-3 : 4-di*iso*propylidene mannitol with a limited amount of allyl bromide and excess alkali. Removal of the *iso*propylidene residues from the product by acid hydrolysis gave a syrup from which 1-allyl mannitol was obtained in small yield. Acetylation of the material remaining in the mother-liquors gave a syrupy product, and determination of the acetyl content and of the unsaturation showed that this was a mixture of mono- and di-allyl compounds. On long storage, crystals separated, and after purification these were found to have the analysis expected for a penta-acetyl monoallyl mannitol. The material was not identical with penta-acetyl 1-allyl mannitol (VIII), and must therefore be *penta-acetyl* 2(or 5)-*allyl mannitol* (X).

For the projected preparation of 3-(2 : 3-dimercaptopropyl) mannitol, the starting material was 1 : 2-5 : 6-di*iso*propylidene mannitol (Baer, *J. Amer. Chem. Soc.*, 1945, 67, 338). This was allylated with 1·4 moles of allyl bromide and excess of alkali, to give 3-*allyl* 1 : 2-5 : 6-*di*iso*propylidene mannitol* (XI). Monoallylation in this case is facilitated by the fact that only one monoallyl derivative is possible, since the 3- and the 4-position in mannitol are identical. Acid hydrolysis of (XI) gave crystalline 3-allyl mannitol, the properties of which agreed well with those given by Wrigley and Yanovsky (*J. Amer. Chem. Soc.*, 1948, 70, 2194) who obtained it as a by-product in the preparation of 3 : 4-diallyl mannitol. It was converted into the *penta-acetyl* derivative (XII) and thence into *penta-acetyl* 3-(2 : 3-*dibromopropyl*) *mannitol*. The corresponding bisthiolacetate was not obtained pure.

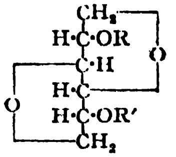
The starting material for the preparation of the 2 : 3-dimercaptopropyl ether of 1 : 4-3 : 6-dianhydromannitol was 1 : 4-3 : 6-dianhydromannitol (XIII) itself, which was prepared from mannitol by the methods of Wiggins (*J.*, 1945, 5) and of Bladon and Owen (preceding paper). Attempts at the direct monoallylation of this compound, with allyl bromide and excess of alkali, all yielded mainly the diallyl compound. The method which was finally used involved conversion of the dianhydromannitol into its monosodium derivative by treatment with sodium in liquid ammonia, and refluxing of the dry sodium salt with excess of allyl bromide in benzene. A mixture of mono- and di-allyl compounds again resulted, but the proportion of monoallyl compound was considerably higher. The mixture was heated with phthalic anhydride in pyridine (method of Levene and Mikeska, *J. Biol. Chem.*, 1927, **75**, 587), and the reaction product was treated with aqueous sodium carbonate solution; the alkali-insoluble portion consisted of 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol, whilst the alkali-soluble portion, on acidification, gave solid *2-allyl* 1 : 4-3 : *6-dianhydromannitol 5-(hydrogen phthalate)* (XIV). The diallyl compound had properties agreeing with those described by Gregory and Wiggins (*J.*, 1947, 1405). The hydrogen phthalate on hydrolysis gave *2-allyl* 1 : 4-3 : *6-dianhydromannitol* (XV) as a liquid, only slightly more viscous than the diallyl compound and of almost identical boiling point. Acetylation of (XV) gave the *acetyl* derivative, which readily took up bromine in carbon tetrachloride solution to give *5-acetyl* 2-(2 : *3-dibromopropyl*) 1 : 4-3 : *6-dianhydromannitol*; treatment of this with potassium thiolacetate in boiling alcohol gave *triacetyl* 2-(2 : *3-dimercaptopropyl*) 1 : 4-3 : *6-dianhydromannitol* (XVI). Finally, almost pure 2-(2 : *3-dimercaptopropyl*) 1 : 4-3 : *6-dianhydromannitol* (XVII) was obtained by deacetylation of the thiolacetate with methanolic hydrogen chloride. The free dithiol was a viscid liquid, readily soluble in water.



(XII).



(XIII; R = H, R′ = H.)
(XIV; R = $CH_2{\cdot}CH{:}CH_2$, R′ = $CO{\cdot}C_6H_4{\cdot}CO_2H$.)
(XV; R = $CH_2{\cdot}CH{:}CH_2$, R′ = H.)
[XVI; R = $CH_2{\cdot}CH(SAc){\cdot}CH_2{\cdot}SAc$, R′ = Ac.]
[XVII; R = $CH_2{\cdot}CH(SH){\cdot}CH_2{\cdot}SH$, R′ = H.]



(XVIII; R = R′ = H.)
(XIX; R = $CH_2{\cdot}CH{:}CH_2$, R′ = H.)
(XX, R = H, R′ = $CH_2{\cdot}CH{:}CH_2$.)

The analogous allylation of the monosodium derivative of 1 : 4-3 : 6-dianhydrosorbitol (XVIII) (Montgomery and Wiggins, *J.*, 1946, 390) gave, by use of the hydrogen phthalate method of separation, 2 : 5-diallyl 1 : 4-3 : 6-dianhydrosorbitol (Gregory and Wiggins, *loc. cit.*) and a liquid which was probably a mixture of the isomeric 2- (XIX) and 5-allyl 1 : 4-3 : 6-dianhydrosorbitol (XX); this mixture yielded a mixture of the corresponding acetyl derivatives on acetylation. Since the two isomers could not be separated, the synthesis was not carried beyond this stage.

EXPERIMENTAL.

(Light absorptions, in ethanol, were determined by Dr. E. A. Braude.)

1 : 3-2 : *4-Diethylidene Sorbitol.*—Appel's method of preparation (*J.*, 1935, 425) was slightly modified and applied to sorbitol (500 g.), paraldehyde (500 c.c.), and concentrated hydrochloric acid (170 c.c.). After 8 hours' stirring, the mixture was extracted twice with chloroform (300 c.c., 100 c.c.), and the extracts were washed with 200-c.c. portions of water, 10% aqueous sodium hydroxide (twice), and with water again, and dried ($CaCl_2$). The chloroform and most of the excess of paraldehyde were removed by distillation under reduced pressure. The residual syrup was heated with acetic acid (400 c.c.) and water (400 c.c.) on the steam-bath under reflux and under reduced pressure (*ca.* 150 mm.) for 2 hours, the liberated acetaldehyde being removed by a current of air drawn through a capillary leak. The solution was concentrated under reduced pressure until solid began to separate; dilution with water then precipitated triethylidene mannitol (30—40 g.), m. p. 165—167° (after recrystallisation from ethanol), derived from mannitol present as impurity in commercial sorbitol (cf. Bourne and Wiggins, *J.*, 1948, 1933). Evaporation of the aqueous solution gave a syrup, which was taken up in methanol (250 c.c.), and treated with ether (100 c.c.) and light petroleum (b. p. 40—60°) (50 c.c.). 1 : 3-2 : 4-Diethylidene sorbitol crystallised as a fine powder when the solution was kept at 0° for a few days; yield, 120—170 g.; m. p. 210—214°.

Allylation of 1 : 3-2 : *4-Diethylidene Sorbitol.*—A mixture of the diethylidene sorbitol (23·5 g., 0·1 mol.), acetone (105 c.c.), sodium hydroxide (32 g.), and water (82 g.) was stirred vigorously in a 1-l. 3-necked flask, fitted with mercury-sealed stirrer, reflux condenser, and dropping-funnel, and surrounded by a water-bath at 70°, whilst a solution of allyl bromide (15 g., 0·125 mol.) in acetone (25 c.c.) was added during 2 hours. Heating and stirring were continued for a further 2 hours, and the condenser was then rearranged for distillation; the water-bath was slowly heated to 100°, whilst a stream of nitrogen was blown through the solution to remove volatile material. The contents of the flask were diluted with water (250 c.c.), and the alkali was partly neutralised with sulphuric acid (16·2 c.c. of concentrated acid in 50 c.c. of water). The reaction product was isolated by 5 extractions with ether (total, 350 c.c.), and the dried (K_2CO_3) extracts were evaporated; distillation of the residue gave 12·3 g. (45%) of a very viscous oil, b. p. 120°/0·005 mm., n_D^{25} 1·4730, $[\alpha]_D^{26}$ −7·5° (*c*, 4 in chloroform), $[\alpha]_D^{22}$ −4·2° (*c*, 4 in ethanol), which was a mixture of mono- and di-allyl compounds (Found: C, 58·2; H, 8·1. Calc. for $C_{12}H_{22}O_6$: C, 56·9; H, 8·1. Calc. for $C_{16}H_{26}O_6$: C, 61·1; H, 8·3%).

1 : 3-2 : 4-*Diethylidene* 5 : 6-*Anhydrosorbitol*.—6-Tosyl 1 : 3-2 : 4-diethylidene sorbitol was prepared by the method of Vargha and Puskás (*Ber.*, 1943, **76**, 859) and crystallised from ethyl acetate–light petroleum (b. p. 60—80°) (cf. Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837); yield, 32%; m. p. 87—90° (Vargha and Puskás, *loc. cit.*, give m. p. 92°).

1 : 3-2 : 4-Diethylidene 5 : 6-anhydrosorbitol was made by the action of sodium methoxide on the 6-tosyl compound (Vargha and Puskás, *loc. cit.*). The yield of almost pure material (m. p. 129—130°) (93%) was much higher than that obtained by these workers, and by Sullivan (*loc. cit.*) (see also the method of preparation given by Wiggins, *J.*, 1946, 388). The anhydro-compound was also made, in almost identical overall yield (28%), by treatment of the crude tosyl compound (syrup) with sodium methoxide; in this case it was isolated by sublimation at 120—140° (bath)/10 mm.

1 : 3-2 : 4-*Diethylidene* 6-*Allyl Sorbitol*.—1 : 3-2 : 4-Diethylidene 5 : 6-anhydrosorbitol (11·5 g.) was heated on the steam-bath for 6½ hours under reflux with a solution of sodium (1 g.) in allyl alcohol (50 c.c.). After addition of water (100 c.c.), the alkali was neutralised with carbon dioxide. Most of the allyl alcohol was removed by distillation under reduced pressure, and after the addition of sodium chloride the solution was extracted 7 times with ether (total 290 c.c.). The extracts were dried (K_2CO_3) and the solvent was removed. Distillation of the very viscous oil gave 1 : 3-2 : 4-*diethylidene* 6-*allyl sorbitol* (10·2 g., 55%), b. p. 115—130° (bath)/0·0001 mm., n_D^{19} 1·4780, $[\alpha]_D^{20}$ −1·3° (*c*, 3 in ethanol) (Found: C, 56·7; H, 8·35. $C_{12}H_{22}O_6$ requires C, 56·9; H, 8·1%).

Penta-acetyl 6-*Allyl Sorbitol*.—6-Allyl 1 : 3-2 : 4-diethylidene sorbitol (10·2 g.) was heated with 4% sulphuric acid (100 c.c.) and ethanol (25 c.c.) on the steam-bath for 5 hours, the liberated acetaldehyde being allowed to escape. The solution was extracted once with ether to remove oily impurities, and then neutralised with barium carbonate (20 g.). The barium salts were removed, and the aqueous solution was evaporated under reduced pressure. The syrup was dried by several evaporations with small amounts of ethanol, and was then dissolved in ethanol (20 c.c.), filtered from a small quantity of insoluble matter, evaporated, and finally dried over phosphoric oxide under reduced pressure. This 6-allyl sorbitol (8·35 g.) failed to crystallise, and it was therefore heated with acetic anhydride (42 c.c.) and fused sodium acetate (4·2 g.) on the steam-bath for 8 hours. Excess of anhydride was removed by distillation under reduced pressure, and the residue was stirred with water for 1½ hours. The product was an oil (14·9 g., 92%) which failed to crystallise, and was distilled. *Penta-acetyl* 6-*allyl sorbitol* had b. p. 140° (bath)/0·0001 mm., n_D^{22} 1·4548, $[\alpha]_D^{21}$ +0·86° (*c*, 2·7 in chloroform) (Found: C, 52·1; H, 6·8; Ac, 48·4. $C_{19}H_{28}O_{11}$ requires C, 52·8; H, 6·5; Ac, 49·4%).

Penta-acetyl 6-(2 : 3-*Dibromopropyl*) *Sorbitol*.—A solution of penta-acetyl 6-allyl sorbitol (13·9 g.) in carbon tetrachloride (60 c.c.) was stirred vigorously and cooled whilst a solution of bromine (5·4 g.) in carbon tetrachloride (20 c.c.) was added during 4 hours, the temperature being kept at −6° to −8°. Stirring was continued for 15 minutes after all the bromine had been added. The carbon tetrachloride solution was washed with sodium hydrogen carbonate solution (50 c.c.), containing sodium thiosulphate (0·5 g.), and dried (Na_2SO_4). The solvent was removed by distillation, and the syrup evaporated several times with methanol, and finally heated at 80°/0·0001 mm. for an hour; yield of *dibromide*, 17·6 g. (93%) (Found: Br, 27·2. $C_{19}H_{28}O_{11}Br_2$ requires Br, 27·0%).

Hepta-acetyl 6-(2 : 3-*Dimercaptopropyl*) *Sorbitol*.—The above dibromide (17 g.), potassium thiolacetate (8 g.), ethanol (60 c.c.), and thiolacetic acid (0·2 c.c.) were heated together on the steam-bath in a 3-necked flask, fitted with reflux condenser, mercury-sealed stirrer, and nitrogen-inlet tube. Vigorous stirring was necessary to prevent violent bumping (caused by precipitated potassium bromide). A slow stream of dry nitrogen was passed through the apparatus during the reaction (6 hours); the deep-yellow solution was then treated with water (300 c.c.), and the insoluble oil was isolated by extraction with ether. The dried (Na_2SO_4) extracts were evaporated in a stream of nitrogen, and the residual syrup was heated to constant weight at 70°/0·0001 mm., to give *hepta-acetyl* 6-(2 : 3-*dimercaptopropyl*) *sorbitol* (16·1 g., 97%) (Found: S, 11·2. $C_{23}H_{34}O_{13}S_2$ requires S, 11·0%). Light absorption: max. 2280 A.; $\varepsilon = 7800$.

Deacetylation. A solution of the hepta-acetate (15·6 g.) in dry methanol (150 c.c.) was cooled to *ca.* −20° and vigorously stirred during addition of methanolic barium methoxide (62 c.c.; 1·04N.), air being excluded by a slow stream of dry nitrogen. After 25 minutes, a fine yellow precipitate suddenly appeared, and after a further 40 minutes it was filtered off in an atmosphere of nitrogen, washed well with methanol and with dry ether, and dried under reduced pressure, first over calcium chloride and finally over phosphoric oxide. The crude barium salt of 6-(2 : 3-dimercaptopropyl) sorbitol (8·4 g.) had $[\alpha]_D^{17}$ +3·15° (*c*, 5 in water) (Found: C, 32·0; H, 6·3; S, 11·2; thiol S, 10·7; Ba, 24·3. Calc. for $C_9H_{18}O_6S_2Ba$: C, 25·5; H, 4·3; S, 15·1; Ba, 32·4%). It formed a fine yellow deliquescent powder, easily soluble in water, and was used without further purification for pharmacological tests. The analytical figures suggest either tenacious retention of solvent or incomplete deacetylation; a triacetate, $C_{15}H_{24}O_9S_2Ba$, requires C, 32·7; H, 4·4; S, 11·7; Ba, 25·0%. The high thiol value, compared with the total sulphur content, indicates almost complete deacetylation of the acetylthio-groups, however.

1 : 2-3 : 4-*Di*iso*propylidene* 5 : 6-*Anhydromannitol*.—1 : 2-3 : 4-Di*iso*propylidene mannitol (Wiggins, *J.*, 1946, 13) (50 g.) was dissolved in dry pyridine (100 c.c.), and a solution of toluene-*p*-sulphonyl chloride (38 g.) in pyridine (70 c.c.) was added, with stirring, during 1 hour, the temperature being kept below 10° by ice-cooling. The mixture was set aside overnight and then concentrated under reduced pressure. Water and chloroform were added, and the chloroform layer was removed and washed successively with dilute hydrochloric acid, water, and sodium hydrogen carbonate solution, and then dried (Na_2SO_4). This solution was cooled to 0° and gradually treated below 5° with a solution of sodium (4·5 g.) in dry methanol (80 c.c.); after a further 10 minutes at 5°, water was added to dissolve the precipitated sodium toluene-*p*-sulphonate, the chloroform layer was removed, and the aqueous portion was extracted once more with chloroform. The combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated to a syrup. Distillation then furnished 1 : 2-3 : 4-di*iso*propylidene 5 : 6-anhydromannitol (27 g., 63%), b. p. 98°/0·003 mm., n_D^{20} 1·4500.

6-Allyl 1 : 2-3 : *4-Di*iso*propylidene Mannitol.*—A solution of the anhydro-compound (25 g.) in allyl alcohol (100 c.c.) containing sodium (4 g.) was boiled under reflux for 6 hours and then concentrated to small bulk. After dilution with water, and neutralisation with hydrochloric acid, the lower oily layer was taken up in chloroform, and the aqueous portion was extracted twice with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to an oil, which on distillation gave *6-allyl* 1 : 2-3 : *4-di*iso*propylidene mannitol* (28 g., 90%), b. p. 140—142°/0·003 mm., n_D^{20} 1·4570 (Found : C, 59·9; H, 8·7. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·7%).

1-*Allyl Mannitol.*—6-Allyl 1 : 2-3 : 4-di*iso*propylidene mannitol (26 g.), suspended in N-sulphuric acid (50 c.c.), was heated on the steam-bath for 4 hours (the solution became homogeneous after ½ hour). The cooled solution was neutralised with barium carbonate, filtered, and evaporated to a solid residue (18 g., 94%) of 1-*allyl mannitol*, which could be crystallised in small quantities from ethanol in the form of plates, m. p. 99—101°, $[\alpha]_D^{22}$ +18° (*c*, 1 in water) (Found : C, 48·0; H, 8·3. $C_9H_{18}O_6$ requires C, 48·6; H, 8·2%). When heated in ethanol for several minutes it appeared to undergo polymerisation, a flocculent precipitate being slowly formed.

Penta-acetyl 1-*Allyl Mannitol.*—1-Allyl mannitol (17 g.) was heated on the steam-bath for 2 hours with acetic anhydride (70 c.c.) and fused sodium acetate (10 g.). The solution was concentrated under reduced pressure and then stirred with water to decompose any remaining anhydride. The oil was taken up in chloroform, and the aqueous solution was extracted once more with chloroform. The combined extracts were washed with water, and with sodium hydrogen carbonate solution, and were then dried (Na_2SO_4) and evaporated to an oil (31 g., 94%), which slowly crystallised. Recrystallisation from methanol gave needles of *penta-acetyl* 1-*allyl mannitol*, m. p. 63—64°, $[\alpha]_D^{17}$ +30° (*c*, 2·3 in chloroform) (Found : C, 52·4; H, 6·7. $C_{19}H_{28}O_{11}$ requires C, 52·7; H, 6·5%).

Penta-acetyl 1-(2 : 3-*Dibromopropyl*) *Mannitol.*—The above penta-acetate (30·2 g.) was dissolved in carbon tetrachloride (100 c.c.) and treated at 0° with bromine (11 g.), added slowly during 1½ hours with stirring. Chloroform (20 c.c.) was then added to dissolve a small amount of oil which had separated, and the solution was washed with sodium hydrogen carbonate solution and then with sodium hydrogen sulphite solution, and finally dried (Na_2SO_4) and evaporated to a pale yellow syrup (41 g., 99%), which consisted essentially of *penta-acetyl* 1-(2 : 3-*dibromopropyl*) *mannitol* (Found : Br, 26·6. $C_{19}H_{28}O_{11}Br_2$ requires Br, 27·0%).

Hepta-acetyl 1-(2 : 3-*Dimercaptopropyl*) *Mannitol.*—The dibromide (41 g.) and potassium thiolacetate (19 g.) in ethanol (200 c.c.) were heated under reflux for 6 hours and then set aside overnight. Water (600 c.c.) was added, most of the alcohol was removed by distillation under reduced pressure, and the product was extracted with ether. The dried ($CaCl_2$) extracts were evaporated to a brown syrup of the *hepta-acetyl* compound (40·5 g., 100%) (Found : S, 10·5. $C_{22}H_{34}O_{12}S_2$ requires S, 11·0%).

Deacetylation. The hepta-acetate (20 g.) in dry methanol (55 c.c.) was treated, as previously described, with 1·13N-barium methoxide (80 c.c.) and gave a crude barium salt (15 g.) (Found : S, 11·2; thiol S, 9·5. Calc. for $C_9H_{18}O_6S_2Ba$: S, 15·1%).

Direct Allylation of 1 : 2-3 : *4-Di*iso*propylidene Mannitol.*—1 : 2-3 : 4-Di*iso*propylidene mannitol (7 g.) in acetone (40 c.c.), sodium hydroxide (10 g.), and water (15 c.c.) was treated at 70° with allyl bromide (4·6 g.) in acetone (10 c.c.) under conditions similar to those described above for 1 : 3-2 : 4-diethylidene sorbitol. The product, isolated by ether-extraction, was distilled, and gave an oil (5·3 g.), b. p. 160°/0·007 mm., n_D^{25} 1·4570, $[\alpha]_D^{22}$ +14·2° (*c*, 5 in chloroform), which was a mixture of mono- and di-allyl compounds (Found : C, 60·8; H, 8·6. Calc. for $C_{15}H_{26}O_6$: C, 59·6; H, 8·7. Calc. for $C_{18}H_{30}O_6$: C, 63·2; H, 7·0%).

This mixture (5 g.) was hydrolysed by being heated with 3% aqueous sulphuric acid for 1½ hours, a little alcohol being added to effect dissolution. The cooled solution was extracted once with ether to remove oily impurities, and the acid was neutralised with barium carbonate (4 g.). The barium salts were removed by filtration, and the aqueous solution was evaporated under reduced pressure from a water-bath at 75°. The syrup was taken up in hot ethanol and filtered. Evaporation of the solvent, and addition of ethyl acetate to the residue, gave a solid (2·6 g.), m. p. 59—80°, which on recrystallisation from acetone, and ethanol–ethyl acetate, gave 1-allyl mannitol, m. p. 98—101°, $[\alpha]_D^{22}$ +17·6° (*c*, 0·8 in water), identical with that prepared *via* the 5 : 6-anhydro-compound.

Evaporation of the mother-liquors gave a syrup (2·6 g.), which was acetylated by being heated on the steam-bath with acetic anhydride (10 c.c.) and fused sodium acetate (2 g.) for 4 hours. Excess of anhydride was decomposed by stirring the mixture with water (100 c.c.) for 2 hours, and the acetyl derivative was isolated by 3 extractions with chloroform. The extracts were washed with sodium hydrogen carbonate solution, the washings being extracted twice with fresh chloroform. The dried (Na_2SO_4) extracts were evaporated, and the residue was distilled to give a colourless syrup (4·1 g.), b. p. 140°/0·0001 mm., n_D^{20} 1·4534, $[\alpha]_D^{18}$ +24·4° (*c*, 4 in chloroform) (Found : Ac, 43·8; equiv., from unsaturation value with ICl, 158. Calc. for monoallyl penta-acetate, $C_{19}H_{28}O_{11}$: Ac, 49·8; equiv., 216. Calc. for diallyl tetra-acetate, $C_{20}H_{30}O_{10}$: Ac, 40·0%; equiv., 107·5). After one month, the syrup deposited crystals (0·6 g.), m. p. 39—54°, which were drained on porous tile. Six recrystallisations from light petroleum (b. p. 60—80°) gave *penta-acetyl 2-allyl mannitol*, m. p. 78—79°, $[\alpha]_D^{21}$ +18·2° (*c*, 1 in chloroform) (Found : C, 52·9; H, 6·4. $C_{19}H_{28}O_{11}$ requires C, 52·8; H, 6·5%). The material depressed the m. p. of penta-acetyl 1-allyl mannitol (m. p. 63—64°) to 54—55°.

Allylation of 1 : 2-5 : *6-Di*iso*propylidene Mannitol.*—1 : 2-5 : 6-Di*iso*propylidene mannitol (Baer, *loc. cit.*) (22·6 g., 0·09 mol.) in water (20 c.c.) and acetone (85 c.c.) was treated with sodium hydroxide solution (32 g. of NaOH in 32 c.c. of water). The mixture, which formed two layers, was vigorously stirred and heated in a water-bath at 75° during addition (4 hours) of a solution of allyl bromide (15·1 g., 0·125 mol.) in acetone (20 c.c.). After working up in the usual way, ether extraction gave an oil, which on distillation furnished *3-allyl* 1 : 2-5 : *6-di*iso*propylidene mannitol* (23 g., 87%), b. p. 139°/0·001 mm., n_D^{19} 1·4562, $[\alpha]_D^{19}$ +5·3° (*c*, 1·0 in chloroform) (Found : C, 59·9; H, 8·7. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·7%).

3-*Allyl Mannitol.*—3-Allyl 1 : 2-5 : 6-di*iso*propylidene mannitol (23 g.) was heated with 6% aqueous sulphuric acid (100 c.c.) on the steam-bath for 4 hours. The solution was cooled, and extracted once with ether to remove oily impurities, and then neutralised with barium carbonate (40 g.) and filtered;

the residue was well washed with hot water. The aqueous solution was evaporated under reduced pressure from a water-bath at 75°, and the residue so obtained was dried by evaporation several times with ethanol. The semi-solid product (16 g.) was dissolved in hot ethanol and filtered from a small amount of insoluble material. Evaporation of the alcoholic solution until crystals formed,and addition of ethyl acetate, gave 3-allyl mannitol (10 g., 59%), m. p. 112—114°; when recrystallised from ethanol–ethyl acetate it formed hard rosettes, m. p. 117°, $[\alpha]_D^{20}$ +15·3° (*c*, 1·0 in water) (Found : C, 48·3; H, 8·2. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2%). Wrigley and Yanovsky (*loc. cit.*) give m. p. 119—120° (corr.), $[\alpha_D^{25}]$ +15·8° (*c*, 4 in water). Evaporation of the mother-liquors gave a syrup (4·5 g.).

Penta-acetyl 3-Allyl Mannitol.—3-Allyl mannitol (9·5 g.), acetic anhydride (38 c.c.), and fused sodium acetate (4·25 g.) were heated together on the steam-bath for 2½ hours. Most of the excess anhydride was removed by distillation under reduced pressure, and the residue was stirred with water for 30 minutes. The insoluble syrup was taken up in chloroform (5 × 50 c.c.), and the extracts were washed with sodium hydrogen carbonate solution, the washings being extracted twice more with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield *penta-acetyl 3-allyl mannitol* (18·4 g., 100%), which distilled as a colourless oil, b. p. 120—150° (bath)/0·001 mm., n_D^{20} 1·4532, $[\alpha]_D^{22}$ +33·3° (*c*, 3 in chloroform) (Found : C, 52·4; H, 6·4; Ac, 51·0; equiv., by ICl titration, 214. $C_{19}H_{28}O_{11}$ requires C, 52·8; H, 6·5; Ac, 49·4; equiv., 216).

Penta-acetyl 3-(2 : 3-*Dibromopropyl*) *Mannitol.*—A solution of penta-acetyl 3-allyl mannitol (2·2 g.) in carbon tetrachloride (15 c.c.) was treated with bromine (0·85 g.) in carbon tetrachloride (15 c.c.), added with vigorous stirring during 2 hours, the temperature being kept below 0°. The solution was then shaken with aqueous sodium thiosulphate, dried (Na_2SO_4), and evaporated, to yield *penta-acetyl* 3-(2 : 3-*dibromopropyl*) *mannitol* as a syrup (2·8 g., 94%), n_D^{23} 1·4794 (Found : Br, 27·4. $C_{19}H_{28}O_{11}Br_2$ requires Br, 27·0%).

Treatment of the dibromide with potassium thiolacetate in the usual way, followed by deacetylation of the liquid bisthiolacetate with barium methoxide, gave the crude barium salt of the dithiol as a pale yellow powder, readily soluble in water. The analysis was typical of this type of compound (Found : S, 11·5; thiol S, 10·1; Ba, 28·1. Calc. for $C_9H_{18}O_6S_2Ba$: S, 15·15; Ba, 32·4%).

Allylation of 1 : 4-3 : 6-*Dianhydromannitol.*—(*a*) A mixture of 1 : 4-3 : 6-dianhydromannitol (Wiggins, *J.*, 1945, 5; Bladon and Owen, preceding paper) (14·6 g., 0·1 mol.), acetone (100 c.c.), sodium hydroxide (36 g.), and water (70 c.c.) was treated at 60—70° with a solution of allyl bromide (15·1 g., 0·125 mol.) in acetone (30 c.c.) during 1½ hours with vigorous stirring. Heating and stirring were continued for a further 2 hours, and the product was then isolated as previously described, giving an oil (4·2 g.), b. p. 160°/10 mm., n_D^{23} 1·4850 (Found : equiv., by ICl titration, 54. Calc. for diallyl derivative, $C_{12}H_{18}O_4$: equiv., 56·5).

The aqueous solution from the ether-extraction was evaporated to dryness under reduced pressure, and the solid residue was extracted with chloroform (Soxhlet). Evaporation of the dried (Na_2SO_4) extracts gave unchanged 1 : 4-3 : 6-dianhydromannitol (8 g.), m. p. and mixed m. p. 83—85°, after recrystallisation from ethyl acetate.

(*b*) A mixture of 1 : 4-3 : 6-dianhydromannitol (29·2 g., 0·2 mol.), dioxan (100 c.c.), sodium hydroxide (72 g.), and water (92 c.c.) was similarly treated at 70° with allyl bromide (30 g., 0·25 mol.) in dioxan (30 c.c.), and gave a product (14·5 g.), b. p. 145°/16 mm., n_D^{26} 1·4802, $[\alpha]_D^{26}$ +157° (*c*, 2 in chloroform), which also consisted largely of 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol (Found : C, 62·6; H, 8·2; equiv., by ICl titration, 59·6. Calc. for $C_{12}H_{18}O_4$: C, 63·7; H, 8·0%; equiv., 56·5). Gregory and Wiggins (*J.*, 1947, 1405) give b. p. 173°/10 mm., n_D^{21} 1·4847, $[\alpha]_D^{23}$ +160° (*c*, 1·5 in chloroform).

(*c*) Sodium (4·6 g., 0·2 atom), in small pieces, was added to a solution of 1 : 4-3 : 6-dianhydromannitol (29·2 g., 0·2 mol.) in liquid ammonia (500 c.c.) contained in a 1-l. flask. The sodium dissolved with evolution of hydrogen. After 1 hour, the small amount of undissolved sodium was removed, the ammonia was boiled off on the steam-bath, and the residual solid was heated under reduced pressure to remove the last traces of ammonia. The fine white powder was transferred to a 500-c.c. flask, fitted with a mercury-sealed stirrer and reflux condenser, and was heated on the steam-bath with dry benzene (100 c.c.) and allyl bromide (50 g.) for 22 hours, with stirring, a further 25 g. of allyl bromide being added after 12 hours. The reaction mixture was treated with water (200 c.c.), the benzene layer was separated, and the aqueous solution was acidified with hydrochloric acid and continuously extracted with ether for 12 hours. The benzene and the ether extracts were dried (Na_2SO_4) and evaporated, yielding oils weighing, respectively, 10·75 g. and 13·1 g. Distillation of the combined oils gave a main fraction (20·5 g.), b. p. 107—115°/1 mm., n_D^{20} 1·4901 (Found : equiv., by ICl titration, 77; corresponding to a mixture containing *ca.* 45% of monoallyl derivative).

This mixture (20 g.) was heated under reflux with phthalic anhydride (16·8 g.) and dry pyridine (50 c.c.) for 23 hours. The excess of pyridine was removed by distillation under reduced pressure, and the residue was taken up in chloroform (100 c.c.) and washed successively with 2N-hydrochloric acid, water, 2N-sodium carbonate, and water. The chloroform solution was dried (Na_2SO_4) and evaporated to a mobile liquid (7·1 g.), which on distillation gave 2 : 5-diallyl 1 : 4-3 : 6-dianhydromannitol (6·3 g.), b. p. 87—89°/0·05 mm., n_D^{22} 1·4842, $[\alpha]_D^{21}$ +160° (*c*, 1·7 in chloroform), $[\alpha]_D^{21}$ +141° (*c*, 5·7 in chloroform) (Found : C, 63·6; H, 8·0; equiv., by ICl titration, 57·4. Calc. for $C_{12}H_{18}O_4$: C, 63·7; H, 8·0%; equiv., 56·5).

The acid washings of the chloroform solution were discarded. The sodium carbonate extracts and the final water-washing were acidified to Congo-red with hydrochloric acid and extracted 4 times with chloroform (100-c.c. portions). The extracts were washed once with water, dried (Na_2SO_4), and evaporated to a very viscous syrup (23·1 g.), which solidified on being stirred with ether. The solid (16·9 g.), m. p. 105—110°, was filtered off, and a portion was recrystallised 4 times from ethyl acetate (with charcoal) to give hard prisms of 2-*allyl* 1 : 4-3 : 6-*dianhydromannitol* 5-(*hydrogen phthalate*), m. p. 110°, $[\alpha]_D^{23}$ +80° (*c*, 0·9 in chloroform) (Found : C, 61·05; H, 5·7. $C_{17}H_{18}O_7$ requires C, 61·05; H, 5·4%). The rotation in 2N-sodium hydroxide, $[\alpha]_D^{20}$ +92° (*c*, 0·8), was unchanged after 12 hours at room temperature, showing that the ester was not appreciably hydrolysed under these conditions.

2-*Allyl* 1 : 4-3 : 6-*Dianhydromannitol.*—The foregoing hydrogen phthalate (16·8 g.) was boiled under reflux with sodium hydroxide (6·5 g.) in water (10 c.c.) for 2 hours, and then heated for a further 6 hours on the steam-bath. The solution, diluted with water (50 c.c.) and treated with sodium hydrogen carbonate (4 g.), was exhaustively extracted with ether (12 hours). The dried (Na_2SO_4) extracts yielded, on evaporation, an oil (9·3 g.), which on distillation furnished *2-allyl* 1 : 4-3 : *6-dianhydromannitol* (8·1 g., 86%) as a colourless mobile liquid, b. p. 85°/0·01 mm., n_D^{24} 1·4920, $[\alpha]_D^{20}$ +113° (*c*, 2·2 in chloroform) (Found: C, 58·0; H, 7·7; equiv., by ICl titration, 93. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%; equiv., 93).

5-Acetyl 2-Allyl 1 : 4-3 : *6-Dianhydromannitol.*—2-Allyl 1 : 4-3 : 6-dianhydromannitol (8 g.), acetic anhydride (25 c.c.), and fused sodium acetate (2·5 g.) were heated together on the steam-bath overnight. The mixture was shaken with water (50 c.c.) until the excess of anhydride was destroyed, and the product was isolated by 4 extractions with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, to give an oil (9·3 g.) which on distillation yielded *5-acetyl 2-allyl* 1 : 4-3 : *6-dianhydromannitol* as a colourless mobile liquid (7·7 g., 82%), b. p. 92—93°/0·01 mm., n_D^{19} 1·4769, $[\alpha]_D^{23}$ +185·6° (*c*, 2·5 in chloroform) (Found: C, 58·1; H, 6·9; equiv., by ICl titration, 114·5. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%; equiv., 114).

5-Acetyl 2-(2 : *3-Dibromopropyl*) 1 : 4-3 : *6-Dianhydromannitol.*—5-Acetyl 2-allyl 1 : 4-3 : 6-dianhydromannitol (7·4 g.) in carbon tetrachloride (80 c.c.) was treated with bromine (6 g.) in the same solvent (30 c.c.), added with cooling and stirring during ½ hour, the temperature being kept below −20°. The solution was allowed to warm to room temperature and was diluted with chloroform (40 c.c.) and stirred for a further 20 minutes in order to dissolve some viscid material which had separated. The solution was then washed with sodium hydrogen carbonate solution (50 c.c.) containing sodium thiosulphate (1 g.), then dried (Na_2SO_4) and evaporated. The viscous syrup (11·6 g., 92%) on distillation from a wide-necked retort gave *5-acetyl* 2-(2 : *3-dibromopropyl*) 1 : 4-3 : *6-dianhydromannitol* (9·3 g.), b. p. 120—170° (air-bath)/0·0001 mm., n_D^{26} 1·5241, $[\alpha]_D^{21}$ +116° (*c*, 2·3 in chloroform) (Found: C, 34·1; H, 4·4; Br, 40·9. $C_{11}H_{16}O_5Br_2$ requires C, 34·0; H, 4·2; Br, 41·2%).

Triacetyl 2-(2 : *3-Dimercaptopropyl*) 1 : 4-3 : *6-Dianhydromannitol.*—The above 5-acetyl compound (8·5 g.), potassium thiolacetate (6 g.), and ethanol (30 c.c.) were heated under reflux, with vigorous stirring, under nitrogen for 7 hours. The mixture was poured into water, and the product was isolated by 6 extractions with ether. The extracts were dried (Na_2SO_4) and evaporated, and the product on distillation gave *triacetyl* 2-(2 : *3-dimercaptopropyl*) 1 : 4-3 : *6-dianhydromannitol* (6·2 g.), b. p. 170—180° (air-bath)/0·0001 mm., n_D^{17} 1·5286, $[\alpha]_D^{19}$ +133° (*c*, 2·0 in chloroform) (Found: C, 46·8; H, 5·7; S, 16·7. $C_{15}H_{22}O_7S_2$ requires C, 47·6; H, 5·9; S, 17·0%). Light absorption: max. 2310 A., ε = 8300.

Deacetylation. The bisthiolacetate (5·2 g.) was heated under reflux with 2% methanolic hydrogen chloride (50 c.c.) for 4 hours under nitrogen. During this time, a brilliant purple colour appeared in the solution, reached a maximum intensity after 2 hours, and then faded, so that it had almost disappeared after 4 hours. The solvent was removed by distillation under reduced pressure and the residual syrup was kept for several hours over solid potassium hydroxide, under reduced pressure. On distillation from a retort, it gave, with slight decomposition, 2-(2 : *3-dimercaptopropyl*) 1 : 4-3 : *6-dianhydromannitol* (2·9 g., 83%), as a yellow, viscous, cloudy liquid, b. p. 150° (air-bath)/0·0001 mm., n_D^{21} 1·5492, $[\alpha]_D^{21}$ +84° (*c*, 2·3 in chloroform) (Found: S, 22·7; thiol S, 21·4. $C_9H_{16}O_4S_2$ requires S, 25·4%). It was readily soluble in water.

Allylation of 1 : 4-3 : *6-Dianhydrosorbitol.*—(*a*) Under conditions similar to those used for the direct allylation of 1 : 4-3 : 6-dianhydromannitol in acetone solution, 1 : 4-3 : 6-dianhydrosorbitol (14·6 g.) and allyl bromide (15·1 g.) gave an oil (2·1 g.), b. p. 90°/0·1 mm., n_D^{19} 1·4818 (Found: equiv., by ICl titration, 58), consisting mainly of diallyl derivative. Unchanged dianhydrosorbitol (7 g.) was recovered.

(*b*) 1 : 4-3 : 6-Dianhydrosorbitol (14·6 g., 0·1 mol.) was converted into the sodium derivative by reaction with sodium (2·3 g., 0·1 atom) in liquid ammonia. The dried salt was then treated with allyl bromide (25 g.) in boiling benzene (50 c.c.) as previously described, and the product (9·3 g.), on distillation, gave a mixture of the mono- and di-allyl derivatives, b. p. 100°/0·5 mm., n_D^{20} 1·4850 (Found: equiv., by ICl titration, 72), which was heated with phthalic anhydride (7·15 g.) in dry pyridine (20 c.c.) as before. There were obtained 2 : 5-diallyl 1 : 4-3 : 6-dianhydrosorbitol (3·6 g.), b. p. 90°/0·1 mm., n_D^{17} 1·4804, $[\alpha]_D^{19}$ +99° (*c*, 4·8 in chloroform) (Found: C, 63·8; H, 7·9; equiv., by ICl titration, 57. Calc. for $C_{12}H_{18}O_4$: C, 63·7; H, 8·0%; equiv., 56·5), and allyl 1 : 4-3 : 6-dianhydrosorbitol hydrogen phthalate, a dark brown glass (probably a mixture of isomers) (9·3 g.) which failed to yield any crystalline salts (Found: equiv., by alkali titration, 313·5. Calc. for $C_{17}H_{18}O_7$: equiv., 334). Gregory and Wiggins (*loc. cit.*) for 2 : 5-diallyl 1 : 4-3 : 6-dianhydrosorbitol give b. p. 185°/40 mm., n_D^{21} 1·4812, $[\alpha]_D^{22}$ +93·4° (*c*, 1·8 in chloroform).

The allyl 1 : 4-3 : 6-dianhydrosorbitol hydrogen phthalate (8·7 g.) was boiled under reflux with a solution of sodium hydroxide (2·7 g.) in water (11 c.c.) for 2 hours. The mixture was then diluted with water (30 c.c.), sodium hydrogen carbonate (2 g.) was added, and the liquid was continuously extracted with ether for 40 hours. The extracts were dried (Na_2SO_4) and evaporated to an oil (3·35 g., 70%), which was distilled, and gave allyl 1 : 4-3 : 6-dianhydrosorbitol as a colourless mobile liquid, b. p. 87—90°/0·05 mm., n_D^{21} 1·4891, $[\alpha]_D^{20}$ +15·1° (*c*, 2·5 in chloroform) (Found: C, 58·1; H, 7·75; equiv., by ICl titration, 97. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%; equiv., 93·1).

On acetylation, by the method previously described, using acetic anhydride and sodium acetate, it gave acetyl allyl 1 : 4-3 : 6-dianhydrosorbitol, b. p. 160°/6 mm., n_D^{20} 1·4730, $[\alpha]_D^{20}$ +115° (*c*, 2 in chloroform) (Found: C, 57·65; H, 7·0. Calc. for $C_{11}H_{16}O_5$: C, 57·9; H, 7·1%).

These substances were probably mixtures of the 2- and the 5-allyl compound.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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113. *Dithiols. Part VII. 5 : 6-Sorbitoleen and 1 : 2-Mannitoleen as Intermediates for the Preparation of Dithiols.**

By Peter Bladon and L. N. Owen.

By the action of sodium iodide, in acetone solution, on 5 : 6-ditosyl or 5 : 6-*dimethanesulphonyl* 1 : 3-2 : 4-*diethylidene sorbitol*, 1 : 3-2 : 4-*diethylidene* 5 : 6-*sorbitoleen* is obtained (cf. Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73); similarly 5 : 6-*dimethanesulphonyl* 1 : 2-3 : 4-*diisopropylidene mannitol* gives 1 : 2-3 : 4-*diisopropylidene* 5 : 6-*mannitoleen*. Removal of the protecting groups by acid hydrolysis then yields 5 : 6-*sorbitoleen* and 1 : 2-mannitoleen. Acetylation, followed by addition of bromine and reaction of the *dibromides* with potassium thiolacetate, gives the hexa-acetyl 5 : 6-dithiohexitols as mixtures of stereoisomers.

Addition of hypobromous acid to the tetra-acetates of 5 : 6-sorbitoleen and 1 : 2-mannitoleen, followed by reaction with sodium acetate, gives hexa-acetyl L-iditol and hexa-acetyl D-sorbitol respectively, and thus provides a new method for the interconversion of hexitols.

Experiments directed towards the synthesis of hydroxy-dithiols of the general formula $HO{\cdot}CH_2{\cdot}[CH(OH)]_n{\cdot}CH(SH){\cdot}CH_2{\cdot}SH$ have been described where $n = 0$ (Stocken, *J.*, 1947, 592), and where $n = 1$ and 2 (Evans, Fraser, and Owen, *J.*, 1949, 248). For the synthesis of the corresponding compound where $n = 3$, an unsaturated alcohol $HO{\cdot}CH_2{\cdot}[CH(OH)]_3{\cdot}CH{:}CH_2$ was required, and our attention was therefore directed towards the preparation of the hexitol derivatives, 1 : 2-mannitoleen and 5 : 6-sorbitoleen.

It has been known for some time that there are exceptions to Oldham and Rutherford's rule (*J. Amer. Chem. Soc.*, 1932, **54**, 366) in that secondary toluene-*p*-sulphonyl derivatives in the carbohydrate field will, in certain cases, react with sodium iodide in acetone solution. For example, both the tosyloxy-groups in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydromannitol (Hockett, Fletcher, Goepp, and Sheffield, *ibid.*, 1946, **68**, 930), and one in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydrosorbitol (*idem, ibid.*, p. 927) react with the reagent at 120° (see also Folkers *et al.*, *ibid.*, 1948, **70**, 2325; Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133). Of particular interest is the behaviour of vicinal tosyloxy-groups; Levene and Mehltretter (*Enzymologia*, 1937, **4**, ii, 232) found that when tritosyl glycerol was heated with sodium iodide in acetone all the groups were displaced, with the formation of an unsaturated compound, free iodine, and sodium toluene-*p*-sulphonate. Similar results were obtained by using tetratosyl erythritol (Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95), and in this case the unsaturated product was butadiene. More recently, Karrer, Schick, and Schwyzer (*Helv. Chim. Acta*, 1948, **31**, 784) have shown that the ditosyl derivatives of glyceraldehyde and of its acetal give acraldehyde.

In the hexitol series, a similar reaction was first observed by Hann, Ness, and Hudson (*loc. cit.*), who briefly reported that heating of 5 : 6-ditosyl 1 : 2-3 : 4-dibenzylidene sorbitol with sodium iodide in acetone at 100° resulted in precipitation of sodium toluene-*p*-sulphonate, liberation of iodine, and formation of 1 : 2-3 : 4-dibenzylidene 5 : 6-sorbitoleen. At the time of this publication, the exact nature of the linking of the benzylidene residues in the parent compound was uncertain, but in view of later work (Angyal and Lawler, *J. Amer. Chem. Soc.*, 1944, **66**, 837) the unsaturated compound must be formulated as 1 : 3-2 : 4-dibenzylidene 5 : 6-sorbitoleen (I).

The first stage in the reaction is undoubtedly the replacement of the primary tosyloxy-group by iodine. It is possible that the resulting intermediate product, containing a secondary tosyloxy-group and an iodine atom on adjacent carbon atoms, is unstable and breaks down directly to the unsaturated compound; more probably, however, the secondary tosyloxy-group in this intermediate undergoes replacement to form the vicinal di-iodide, a type of compound which is known to be unstable, and which then loses iodine in the usual way:

$$R{\cdot}CH(OTs){\cdot}CH_2{\cdot}OTs \longrightarrow R{\cdot}CH(OTs){\cdot}CH_2I \longrightarrow R{\cdot}CHI{\cdot}CH_2I \longrightarrow R{\cdot}CH{:}CH_2$$

In utilising this reaction for the preparation of 5 : 6-sorbitoleen, 1 : 3-2 : 4-diethylidene sorbitol was converted into 5 : 6-ditosyl 1 : 3-2 : 4-diethylidene sorbitol (II) (Wiggins, *J.*, 1946, 388; Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837), which reacted readily with sodium iodide in acetone at 100° and gave 1 : 3-2 : 4-*diethylidene* 5 : 6-*sorbitoleen* (III); the same product was also obtained from 5 : 6-*dimethanesulphonyl* 1 : 3-2 : 4-*diethylidene sorbitol* under the same conditions. Removal of the ethylidene residues from (III) by acid hydrolysis gave 5 : 6-*sorbitoleen* (IV) as a viscous liquid which could be distilled in high vacuum without decomposition; the overall yield from ditosyl diethylidene sorbitol was 70—80%. On acetylation, with acetic anhydride and sodium acetate, it gave crystalline *tetra-acetyl* 5 : 6-*sorbitoleen* (V), which took up bromine in carbon tetrachloride solution and gave a *dibromide*, which partly crystallised.

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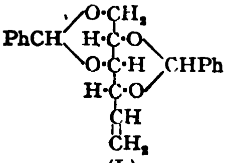
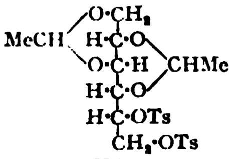
* A preliminary note on part of this work appeared in *Nature*, 1949, **163**, 140.

The addition of bromine to (V) can theoretically give two products, (VI) and (VII), and the solid isomer must correspond to one of these formulæ, the other being present in the liquid portion. There is, however, no means of deciding which formula should be allocated to a particular isomer. The liquid and the crystalline substance were separately treated with potassium thiolacetate in boiling ethanol; both yielded syrups, but that derived from the crystalline dibromide slowly deposited a solid *hexa-acetyl* 5 : 6-*dithiohexitol*, (VIII) or (IX). In the reaction of the dibromides with potassium thiolacetate, partial epimerisation occurs on $C_{(5)}$; the solid product, therefore, does not necessarily possess the same (unknown) configuration as the crystalline dibromide. Deacetylation of the combined thiolacetate syrups with methanolic barium methoxide gave a crude barium salt of the 5 : 6-dithiohexitol (X).


(I.)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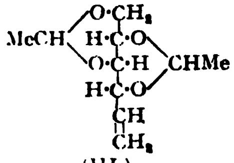
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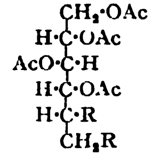
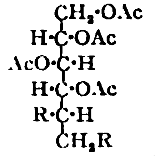

(VI; R = Br.)
(VIII; R = SAc)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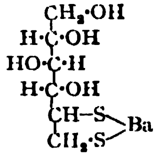
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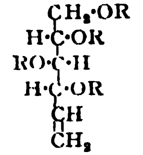
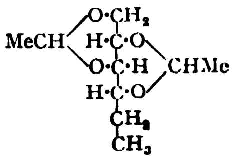

(IV; R = H.)
(V; R = Ac.)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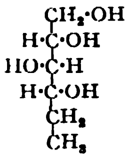
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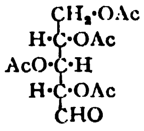
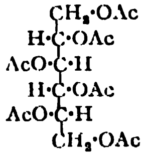
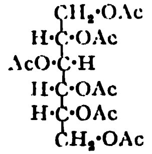

(XIII.)


(XIV.)


(XV.)

Several other reactions were carried out on derivatives of 5 : 6-sorbitoleen. Hydrogenation of 1 : 3-2 : 4-diethylidene 5 : 6-sorbitoleen (III) over Raney nickel gave 1 : 3-2 : 4-*diethylidene* 5 : 6-*dideoxysorbitol* (XI), from which 5 : 6-*dideoxysorbitol* (XII) (*tetra-acetate*) was obtained by acid hydrolysis. Ozonolysis of tetra-acetyl 5 : 6-sorbitoleen (V) afforded a small yield of tetra-acetyl *aldehydo*-L-xylose (XIII) (cf. Major and Cook, *J. Amer. Chem. Soc.*, 1936, **58**, 2474; Wolfrom *et al.*, *ibid.*, 1931, **53**, 4379; 1944, **66**, 204). It was also possible to convert (V) into hexa-acetyl L-iditol; reaction of the unsaturated compound with *N*-bromosuccinimide in water and ether (a convenient source of hypobromous acid; see Raphael, *J.*, 1949, S 44) gave a non-crystalline bromohydrin of uncertain structure, and probably consisting of a mixture of isomers. This, on being heated with sodium acetate in acetic anhydride and acetic acid, gave a syrup from which hexa-acetyl L-iditol (XIV) was obtained in crystalline form; the yield was low, but no evidence was found of the presence of hexa-acetyl sorbitol (XV), the other possible product. Hexa-acetyl L-iditol was also obtained by treatment of the crystalline tetra-acetyl sorbitoleen dibromide, (VI) or (VII), with potassium acetate; this, however, does not prove the configuration of the original dibromide.

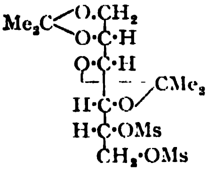
For the preparation of 1 : 2-mannitoleen and its derivatives the starting material was 1 : 2-3 : 4-di*iso*propylidene mannitol (Wiggins, *J.*, 1946, 13). Treatment with methanesulphonyl chloride in pyridine gave crystalline 5 : 6-*dimethanesulphonyl* 1 : 2-3 : 4-*diisopropylidene mannitol* (XVI); the corresponding 5 : 6-*ditosyl* compound was a liquid. When (XVI) was heated in acetone solution with sodium iodide, it gave 1 : 2-3 : 4-*di*iso*propylidene* 5 : 6-*mannitoleen* (XVII) as a mobile liquid. In the distillation of the crude reaction product, free iodine was liberated, indicating the presence of an iodine-containing compound, comparatively stable at moderate temperatures, but broken down when more strongly heated. Furthermore, from the non-volatile residue a small quantity of a water-soluble solid was obtained, which was identified as 1 : 2(or 5 : 6)-mannitoleen (XVIII). The mechanism of the formation of this compound, which involves the loss of the *iso*propylidene residues, is obscure; it appears that it must be produced during the distillation, since it is practically insoluble in chloroform and would not have been extracted from aqueous solution by this solvent during the working-up process. It was obtained in good yield from the di*iso*propylidene compound by acid hydrolysis, the overall yield from the dimethanesulphonyl derivative being 45%.

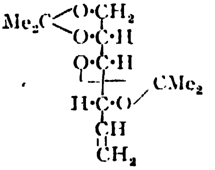
Acetylation of 1 : 2-mannitoleen gave the crystalline tetra-acetate, which reacted with bromine in carbon tetrachloride to give a solid dibromide, which was separated by fractional crystallisation into two *isomers*, m. p.s 111—112° and 76°. The optical rotations of these were almost identical, which suggested that they were polymorphic forms of the same substance, but a mixture of them melted over the range between their individual m. p.s and it was not possible to convert one form into the other. They must therefore be the structural isomers (XIX) and (XX), although there is no means of deciding the individual allocation of formulæ.

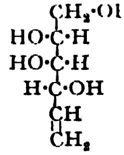
Treatment of both dibromides with potassium thiolacetate in boiling ethanol gave the hexa-acetyl 5 : 6-dithiohexitols, presumably mixtures of (XXI) and (XXII).

Tetra-acetyl 1 : 2-mannitoleen reacted with hypobromous acid to give a liquid bromohydrin, which on treatment with sodium acetate gave hexa-acetyl D-sorbitol (XV); none of the other possible product (hexa-acetyl D-mannitol) was encountered.

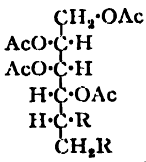
Unsuccessful attempts were made to prepare an unsaturated compound from 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol and from 3 : 4-*dimethanesulphonyl* 1 : 2-5 : 6-*diiso-propylidene mannitol* (XXIII). When these compounds were heated with sodium iodide in acetone at 110°, the sodium sulphonate was obtained in theoretical yield, and iodine was liberated, but none of the expected material could be isolated. Possibly the *iso*propylidene residues were eliminated during the reaction.


(XVI.) (Ms = Me·SO$_2$.)

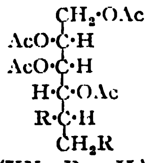

(XVII.)


(XVIII.)

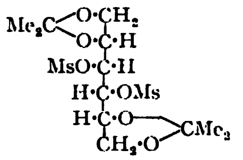
$$\begin{array}{c} CH_2{\cdot}OH \\ HO{\cdot}C{\cdot}H \\ HO{\cdot}C{\cdot}H \\ H{\cdot}C{\cdot}OH \\ CH \\ \| \\ CH_2 \end{array}$$


(XIX; R = Br.)
(XXI; R = SAc.)

$$\begin{array}{c} CH_2{\cdot}OAc \\ AcO{\cdot}C{\cdot}H \\ AcO{\cdot}C{\cdot}H \\ H{\cdot}C{\cdot}OAc \\ H{\cdot}C{\cdot}R \\ CH_2R \end{array}$$


(XX; R = H.)
(XXII; R = SAc.)

$$\begin{array}{c} CH_2{\cdot}OAc \\ AcO{\cdot}C{\cdot}H \\ AcO{\cdot}C{\cdot}H \\ H{\cdot}C{\cdot}OAc \\ R{\cdot}C{\cdot}H \\ CH_2R \end{array}$$


(XXIII.)

Since the completion of this work, Karrer and Davis (*Helv. Chim. Acta*, 1948, **31**, 1611) have reported experiments on the preparation of 1 : 2-mannitoleen from 1 : 2-3 : 4-di*iso*-propylidene mannitol by a method similar to that described above. Their results (with the ditosyl compound), however, differ in some respects from those obtained by us with the dimethanesulphonyl derivative. They found that treatment with sodium iodide in acetone gave 1 : 2-mannitoleen directly, and they failed to isolate the di*iso*propylidene compound, which was the main product in our experiments. Furthermore, the direct yield from the ditosyl di*iso*propylidene mannitol is only half of the overall yield obtained from the dimethane-sulphonate.

EXPERIMENTAL.

5 : 6-*Ditosyl* 1 : 3-2 : 4-*Diethylidene Sorbitol*.—1 : 3-2 : 4-Diethylidene sorbitol (Bladon and Owen, preceding paper) (47 g.) in dry pyridine (250 c.c.) was treated with a solution of toluene-*p*-sulphonyl chloride (80 g., 2·1 mols.) in pyridine (160 c.c.) with cooling, and then set aside at room temperature for 21 hours. Addition of water (1500 c.c.) precipitated a solid, which was washed with water and with ethanol. This ditosyl derivative (45 g.), m. p. 169—170°, was sufficiently pure for most purposes;

further recrystallisation from acetone–ethanol raised the m. p. to 170—172°, $[\alpha]_D^{21}$ $-12{\cdot}0°$ (*c*, 1·7 in chloroform). Wiggins (*loc. cit.*) gives m. p. 173°, $[\alpha]_D$ $-12{\cdot}6°$; Sullivan (*loc. cit.*) gives m. p. 172°, $[\alpha]_D^{23}$ $-12{\cdot}8°$. It was obtained only as a by-product by these workers.

5 : 6-*Dimethanesulphonyl* 1 : 3-2 : 4-*Diethylidene Sorbitol*.—1 : 3-2 : 4-Diethylidene sorbitol (4·7 g.) was added slowly to a cooled solution of methanesulphonyl chloride (5·8 g.) in dry pyridine (12 c.c.). The mixture was set aside at 0° overnight and then diluted with water, which precipitated a viscid oil; a portion crystallised on trituration with methanol, and the main bulk was then seeded. The solid was well washed with water and recrystallised from methanol to give irregular prisms of the *dimethanesulphonate* (5·4 g.), m. p. 152—153°, $[\alpha]_D^{21}$ $-5{\cdot}2°$ (*c*, 1·0 in chloroform) (Found: C, 37·0; H, 6·3; S, 16·3. $C_{12}H_{22}O_{10}S_2$ requires C, 36·9; H, 5·7; S, 16·4%).

1 : 3-2 : 4-*Diethylidene* 5 : 6-*Sorbitoleen*.—(i) The ditosyl compound (41 g.), anhydrous sodium iodide (90 g.), and pure acetone (600 c.c.) were heated in a pressure bottle at 100° for 6 hours. The precipitated sodium toluene-*p*-sulphonate (29·5 g., 100%) was filtered off from the cooled reaction product, and well washed with cold acetone. The dark brown filtrate was evaporated to small bulk, and the residue was shaken with a solution of sodium thiosulphate (37·5 g.) in water (250 c.c.) to remove free iodine. The solution was then extracted with chloroform (4 × 50 c.c.); evaporation of the dried (Na_2SO_4) extracts gave a solid residue (15·4 g.), which on recrystallisation from ethyl acetate gave needles (10·9 g., 73%) of 1 : 3-2 : 4-*diethylidene* 5 : 6-*sorbitoleen*, m. p. 120—122°, raised on further recrystallisation to 122—123°, $[\alpha]_D^{21}$ $-23{\cdot}8°$ (*c*, 1·1 in chloroform) (Found: C, 60·4; H, 7·9. $C_{10}H_{16}O_4$ requires C, 60·05; H, 8·1%).

(ii) Similar treatment of 5 : 6-dimethanesulphonyl 1 : 3-2 : 4-diethylidene sorbitol (1·95 g.) with sodium iodide (6·0 g.) in acetone (40 c.c.) for 6 hours at 100° gave sodium methanesulphonate (1·6 g., 100%), and, from the chloroform extracts, 1 : 3-2 : 4-diethylidene 5 : 6-sorbitoleen (1·0 g.), which on recrystallisation from ethyl acetate formed needles (0·6 g.), m. p. 122—124°.

5 : 6-*Sorbitoleen*.—1 : 3-2 : 4-Diethylidene 5 : 6-sorbitoleen (15 g.) was heated with N-sulphuric acid (10 c.c.) and water (20 c.c.) at 100° for 11 hours under nitrogen. The cooled solution was then extracted once with ether to remove a small amount of oily impurity, and neutralised by the addition of a slight excess of barium hydroxide solution, followed by treatment with carbon dioxide. After being heated, to assist coagulation of the barium sulphate, it was filtered, the solid being well washed with hot water. Evaporation of the filtrate under reduced pressure gave a syrup, which was taken up in hot ethanol (50 c.c.), treated with charcoal, filtered, and evaporated to yield 5 : 6-*sorbitoleen* (10·8 g.), a small portion of which was distilled at 100—130° (air-bath)/0·0001 mm.; n_D^{19} 1·5068, $[\alpha]_D^{19}$ $+19{\cdot}8°$ (*c*, 3·8 in water) (Found: C, 48·5; H, 8·3. $C_6H_{12}O_4$ requires C, 48·6; H, 8·2%).

Tetra-acetyl 5 : 6-*Sorbitoleen*.—5 : 6-Sorbitoleen (7·4 g.) was heated with acetic anhydride (40 c.c.) and fused sodium acetate (5 g.) for 9 hours on the steam-bath. The solution was then poured into cold water (400 c.c.) and well stirred to decompose the excess of acetic anhydride. The *tetra-acetate* separated as a white solid (12·5 g., 80%), which was collected and recrystallised from aqueous methanol; it formed small prisms, m. p. 57—58·5°, $[\alpha]_D^{21}$ $-13{\cdot}6°$ (*c*, 1·2 in chloroform) (Found: C, 52·8; H, 6·2. $C_{14}H_{20}O_8$ requires C, 53·15; H, 6·4%). Extraction of the aqueous solution with chloroform gave a further quantity (2·6 g.) of the same material.

Reaction of Tetra-acetyl 5 : 6-*Sorbitoleen with Bromine*.—A solution of bromine (8·8 g.) in carbon tetrachloride (40 c.c.) was added to a well-stirred and cooled solution of the tetra-acetate (15·8 g.) in the same solvent (150 c.c.), the temperature being kept at *ca.* 15° during the addition (2 hours) and for a further hour. A small quantity of solid which had separated was taken into solution by addition of a little chloroform, and the solution was washed with sodium hydrogen carbonate containing some sodium thiosulphate, and then with water, dried (Na_2SO_4), and evaporated to a syrup (25·7 g.). This was dissolved in warm ethanol (50 c.c.) and cooled to 0°, whereupon a solid crystallised. After being kept at 0° for 12 hours, it was collected and washed with ethanol (yield, 12·1 g.; m. p. 135—145°); recrystallisation from acetone gave small prisms of the *dibromide*, m. p. 152—154°, $[\alpha]_D^{18}$ $-21{\cdot}4°$ (*c*, 1·3 in chloroform) (Found: C, 35·5; H, 4·4; Br, 33·3. $C_{14}H_{20}O_8Br_2$ requires C, 35·3; H, 4·2; Br, 33·6%).

Evaporation of the ethanolic filtrate gave a syrup (10·4 g.), $[\alpha]_D^{21}$ $+7{\cdot}6°$ (*c*, 12 in chloroform), which contained the stereoisomeric dibromide (Found: Br, 32·0%).

Hexa-acetyl 5 : 6-*Dithiohexitol*.—(*a*) The crystalline dibromide (11·9 g.) and potassium thiolacetate (6·8 g.) were heated under reflux in ethanol (125 c.c.) for 7 hours. Water (250 c.c.) was then added, and the mixture was extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave a red syrup, which partly crystallised when kept for a week. The solid (3·5 g.; m. p. 86—87°) was freed from oil by trituration with cold methanol; recrystallisation from methanol then gave flat needles of the *hexa-acetyl* 5 : 6-*dithiohexitol*, m. p. 87—89°, $[\alpha]_D^{21}$ $+49{\cdot}4°$ (*c*, 2·8 in chloroform) (Found: C, 46·5; H, 5·9; S, 13·5. $C_{18}H_{26}O_{10}S_2$ requires C, 46·3; H, 5·6; S, 13·7%). Light absorption: max. 2300 A., $\varepsilon = 7900$.

(*b*) The liquid dibromide (9·8 g.), potassium thiolacetate (5·7 g.), thiolacetic acid (0·3 c.c.), and ethanol (40 c.c.) were heated under reflux for 6 hours. The product, isolated as described above, failed to crystallise, and was distilled, to yield the hexa-acetyl dithiohexitol (7·8 g.), b. p. 140—160°/0·001 mm., n_D^{20} 1·4895, $[\alpha]_D^{21}$ $-17{\cdot}8°$ (*c*, 1·5 in chloroform) (Found: C, 47·4; H, 5·8; S, 13·65%). Light absorption: max. 2290 A., $\varepsilon = 5000$.

Deacetylation. The syrupy hexa-acetate (21·3 g.) was dissolved in methanol (250 c.c.) and treated at −20° with 1·07N-methanolic barium methoxide (103 c.c.), air being excluded. The temperature was then allowed to rise to 0°, and stirring continued for a further 45 minutes. The precipitated barium salt was collected, washed with methanol and with ether, and dried under reduced pressure over calcium chloride and finally over phosphoric oxide; yield, 9·3 g. (Found: C, 28·6; H, 5·4; S, 17·6; thiol S, 10·8; Ba, 26·4. $C_6H_{12}O_4S_2Ba$ requires C, 20·6; H, 3·5; S, 18·4; Ba, 39·3%). The analysis, as usual with these compounds, indicated considerable contamination with other products; earlier work has shown that the deacetylation of acetylated polyhydroxy-dithiols does not proceed smoothly (cf. Part III, *J.*, 1949, 248; Part VI, preceding paper).

1 : 3-2 : 4-*Diethylidene* 5 : 6-*Dideoxysorbitol*.—1 : 3-2 : 4-Diethylidene 5 : 6-sorbitoleen (3 g.) in ethyl acetate (35 c.c.) was hydrogenated at ordinary temperature and pressure over Raney nickel catalyst; the filtered solution was then evaporated to a solid residue (3 g.), m. p. 84—86°. Recrystallisation from

light petroleum (b. p. 60—80°) gave 1 : 3-2 : 4-*diethylidene* 5 : 6-*dideoxysorbitol*, m. p. 85—86°, $[\alpha]_D^{2}$ +7·8° (*c*, 1·7 in chloroform) (Found: C, 59·55; H, 8·6. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%).

5 : 6-*Dideoxysorbitol*.—The diethylidene compound (3 g.) was heated on the steam-bath for 7 hours under reflux with methanol (5 c.c.) and 0·45N-sulphuric acid (10 c.c.). The cooled solution was extracted once with ether to remove a trace of oil, and was heated and treated with a slight excess of barium hydroxide solution, the excess then being removed with carbon dioxide. The barium salts were removed by filtration, and well washed with hot water; evaporation of the filtrate under reduced pressure gave a syrup, which was dissolved in warm methanol, filtered, and again evaporated to give 5 : 6-*dideoxysorbitol* (2·2 g.). A small portion, distilled at 150—160°(bath)/0·0001 mm., had n_D^{24} 1·4825, $[\alpha]_D^{21}$ +5·7° (*c*, 2·0 in water) (Found: C, 47·5; H, 9·5. $C_6H_{14}O_4$ requires C, 48·0; H, 9·4%).

Acetylation of 5 : 6-dideoxysorbitol (1·7 g.) with acetic anhydride (15 c.c.) and sodium acetate (1 g.) at 100° for 12 hours, gave *tetra-acetyl* 5 : 6-*dideoxysorbitol* (3·7 g.), b. p. 100—120°/0·0001 mm., n_D^{21} 1·4415, $[\alpha]_D^{21}$ +6·3° (*c*, 2·6 in chloroform) (Found: C, 53·0; H, 7·3. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·2%).

Tetra-acetyl aldehydo-L-*Xylose*.—Tetra-acetyl 5 : 6-sorbitoleen (0·5 g.) in ethyl acetate (10 c.c.) was treated with a stream of ozonised oxygen at −30° until no more ozone was absorbed. The solution was then shaken with hydrogen, in the presence of Raney nickel (1·5 g.), until no more was absorbed and evaporated under reduced pressure to an oil, which crystallised on the addition of light petroleum (b. p. 40—60°). Recrystallisation from dry ether gave tetra-acetyl *aldehydo*-L-xylose, m. p. 85—87°, $[\alpha]_D^{21}$ +17·6° (*c*, 1·0 in chloroform), which restored the colour to Schiff's reagent. Major and Cook (*loc. cit.*) give m. p. 90—91°, $[\alpha]_D^{20}$ +22·5° (*c*, 2 in absolute chloroform) (cf. also Wolfrom *et al.*, *loc. cit.*).

Hexa-acetyl L-*Iditol*.—(*a*) A solution of tetra-acetyl sorbitoleen (0·53 g) in ether (5 c c.) was shaken with *N*-bromosuccinimide (0·35 g.) and water (15 c.c.) overnight. The ethereal layer was separated, the aqueous portion was extracted twice with ether, and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was heated on the steam-bath with acetic anhydride (1·5 c.c.), acetic acid (1·5 c.c.), and sodium acetate (0·5 g.) for 26 hours (a crystalline precipitate of sodium bromide began to appear after 6 hours) and then stirred with water. The solution was extracted thrice with chloroform, and the extracts were washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to a syrup (0·65 g.), which was dissolved in dry ether containing a little methanol and treated with light petroleum (b. p. 40—60°). Hexa-acetyl L-iditol (0·2 g.) was obtained, m. p. 118—120°, $[\alpha]_D^{22}$ −26·8° (*c*, 1·0 in chloroform). Hann and Hudson (*J. Amer. Chem. Soc.*, 1942, **64**, 925) give m. p. 121—122° (corr.), $[\alpha]_D^{20}$ −25·5° (chloroform); Meyer and Reichstein (*Helv. Chim. Acta*, 1946, **29**, 161) give m. p. 119·5—120·5°, $[\alpha]_D^{19}$ −26·1° ± 2° (*c*, 0·9 in chloroform). Evaporation of the mother-liquors gave a syrup, from which no more solid material could be obtained.

(*b*) The crystalline dibromide of tetra-acetyl 5 : 6-sorbitoleen (0·7 g.; m. p. 152—153°), fused potassium acetate (1·25 g.), acetic acid (7·5 c.c.), and acetic anhydride (2·5 c.c.) were heated on a sand-bath under reflux for 60 hours. The mixture gradually darkened, and a precipitate of potassium bromide slowly appeared. The cooled mixture was then poured into water (40 c.c.) and extracted with chloroform. The extracts were washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to a syrup. This was dissolved in a little methanol and treated with ether and light petroleum (b. p. 40—60°), whereupon crystals (0·2 g.) gradually separated. Recrystallisation from methanol–ether gave hexa-acetyl L-iditol, m. p. (and mixed m. p. with that obtained by the first method) 118—120°, $[\alpha]_D^{17}$ −26·6° (*c*, 1·2 in chloroform).

5 : 6-*Dimethanesulphonyl* 1 : 2-3 : 4-*Di*iso*propylidene Mannitol*.—To a solution of 1 : 2-3 : 4-di*iso*propylidene mannitol (Wiggins, *J.*, 1946, 13) (7·6 g.) in dry pyridine (18 c.c.) was added a solution of methanesulphonyl chloride (8·6 g.) in pyridine (18 c.c.), the temperature being kept below 20°. The mixture was set aside at 0° for 12 hours and then poured into water (250 c.c.). The precipitated oil crystallised on nucleation with a sample which had been caused to solidify by trituration with methanol. The solid was collected and well washed with water. One recrystallisation from methanol gave 10·65 g., m. p. 117—118°. Further recrystallisation from the same solvent gave pure 5 : 6-*dimethanesulphonyl* 1 : 2-3 : 4-*di*iso*propylidene mannitol*, m. p. 118—120°, $[\alpha]_D^{20}$ +25·1° (*c*, 2·0 in chloroform) (Found: C, 39·95; H, 6·3; S, 15·3. $C_{14}H_{26}O_{10}S_2$ requires C, 40·2; H, 6·3; S, 15·3%).

5 : 6-*Ditosyl* 1 : 2-3 : 4-*Di*iso*propylidene Mannitol*.—Similar treatment of 1 : 2-3 : 4-di*iso*propylidene mannitol (1·3 g.) in pyridine (6 c.c.) with toluene-*p*-sulphonyl chloride (2·1 g.) gave an oil on addition of water to the reaction mixture. It was isolated by chloroform extraction; the extracts were washed with hydrochloric acid, sodium hydrogen carbonate solution, and with water, dried (Na_2SO_4), and evaporated to a viscous oil (2·2 g.). This crude *ditosyl* derivative had $[\alpha]_D^{21}$ +12·1° (*c*, 4 in chloroform) (Found: S, 10·6. $C_{26}H_{34}O_{10}S_2$ requires S, 11·2%).

1 : 2-3 : 4-*Di*iso*propylidene* 5 : 6-*Mannitoleen*.—5 : 6-Dimethanesulphonyl 1 : 2-3 : 4-di*iso*propylidene mannitol (14·4 g.), sodium iodide (42 g.), and acetone (280 c.c.) were heated in a pressure bottle at 100° for 6½ hours. The precipitated sodium methanesulphonate (11·1 g.) was filtered off and washed with acetone. The filtrate and washings were evaporated to small bulk, and the residue was stirred with a solution of sodium thiosulphate (20 g.) in water (200 c.c.) and extracted 5 times with chloroform (50-c.c. portions). The dried (Na_2SO_4) extracts were evaporated to an oil (7·6 g.) which was distilled, b. p. 40°/0·1 mm.; the distillate contained free iodine, and it was therefore dissolved in chloroform and washed with sodium thiosulphate solution. The recovered oil on distillation gave colourless 1 : 2-3 : 4-*di*iso*propylidene* 5 : 6-*mannitoleen* (5·2 g.), b. p. 41°/0·1 mm., n_D^{23} 1·4401, $[\alpha]_D^{21}$ −5·5° (*c*, 2·4 in chloroform) (Found: C, 63·4; H, 8·6. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%)

A higher-boiling fraction and the still residue from the first distillation were combined, and oily material and iodine were removed by extraction with chloroform. The crystalline residue, on recrystallisation from methanol saturated with light petroleum (b. p. 40—60°) gave 1 : 2-mannitoleen as short needles, m. p. 147—149°, $[\alpha]_D^{20}$ +30·9° (*c*, 1·0 in water) (Found: C, 48·6; H, 7·9. Calc. for $C_6H_{12}O_4$: C, 48·6; H, 8·2%).

Hydrolysis of 1 : 2-3 : 4-*Di*iso*propylidene* 5 : 6-*Mannitoleen*.—A solution of the di*iso*propylidene compound (5·0 g.) in 0·3N-sulphuric acid (15 c.c.) was heated on the steam-bath for 7 hours in a slow stream of nitrogen. The solution was then cooled and extracted once with ether to remove oily impurities. The acid was neutralised by addition, to the hot solution, of barium hydroxide solution in slight excess, followed by carbon dioxide. The barium salts were filtered off and washed with water, and the filtrate and washings were evaporated under reduced pressure. The solid residue was dissolved in warm methanol (100 c.c.) and the solution was filtered and evaporated, the residue being dried by evaporation with benzene and ethanol. Recrystallisation from ethanol–ethyl acetate gave 1 : 2-mannitoleen (2·25 g.), m. p. 144—148°, raised on further recrystallisation to m. p. 147—148°, $[\alpha]^{20}_{\mathrm{D}}$ +30·0° (*c*, 1·0 in water). Karrer and Davis (*loc. cit.*) give m. p. 148·5—149°, $[\alpha]^{18}_{\mathrm{D}}$ +33·4° (in water).

Tetra-acetyl 1 : 2-*Mannitoleen*.—1 : 2-Mannitoleen (2·0 g.), acetic anhydride (10 c.c.), and fused sodium acetate (1·0 g.) were heated on the steam-bath for 12 hours. The reaction mixture was then poured into water and stirred to decompose excess of anhydride. The mixture was cooled to 0°, and the solid was collected (yield, 4·3 g.; m. p. 79—82°). Recrystallisation from methanol gave plates of the tetra-acetyl derivative, m. p. 80—81°, $[\alpha]^{22}_{\mathrm{D}}$ +49·4° (*c*, 1·0 in chloroform) (Found: C, 53·1; H, 6·0. Calc. for $C_{14}H_{20}O_8$: C, 53·15; H, 6·4%). Karrer and Davis (*loc. cit.*) give m. p. 81·5°.

Reaction of Tetra-acetyl 1 : 2-*Mannitoleen with Bromine*.—A solution of bromine (1·8 g.) in carbon tetrachloride (30 c.c.) was added slowly to a solution of the tetra-acetate (3·15 g.) in carbon tetrachloride (50 c.c.), the temperature being kept below 20°. Stirring was then continued for two hours, and the solution was washed with sodium hydrogen carbonate solution, containing a little sodium thiosulphate. A small quantity of oil, not soluble in the carbon tetrachloride, was brought into solution by addition of some chloroform, and the solution was dried (Na_2SO_4) and evaporated to an oil (4·7 g.). This was dissolved in methanol (12 c.c.), and the solution was cooled to 0°, and kept thereat overnight. The solid (2·1 g.; m. p. 85—100°) was collected and recrystallised from methanol to give the first *dibromide* as hexagonal plates, m. p. 111—112°, $[\alpha]^{21}_{\mathrm{D}}$ +43·8° (*c*, 1·1 in chloroform) (Found: C, 35·5; H, 4·3; Br, 33·1. $C_{14}H_{20}O_8Br_2$ requires C, 35·3; H, 4·2; Br, 33·6%).

The main methanolic filtrate was evaporated to a solid residue, which on recrystallisation twice from light petroleum (b. p. 60—80°) and four times from ethyl acetate–light petroleum (b. p. 60—80°) gave cubes of the isomeric *dibromide*, m. p. 76°, $[\alpha]^{21}_{\mathrm{D}}$ +45·5° (*c*, 1·1 in chloroform) (Found: C, 35·3; H, 4·3; Br, 33·6%).

The first dibromide (1·3 g.; crude) was heated under reflux with a solution of potassium thiolacetate (0·9 g.) in ethanol (15 c.c.) for 8 hours. The bisthiolacetate was isolated in the usual way and formed a syrup (1·1 g.), $[\alpha]^{21}_{\mathrm{D}}$ +25·4° (*c*, 2·6 in chloroform), which failed to crystallise. Light absorption: max. 2290 A., ε = 6500. The second dibromide (1·9 g.), similarly treated, also gave a syrup (1·6 g.), $[\alpha[^{23}_{\mathrm{D}}$ +21·8° (*c*, 3·0 in chloroform); light absorption: max. 2290 A., ε = 7000.

Reaction of Tetra-acetyl 1 : 2-*Mannitoleen with Hypobromous Acid*.—The tetra-acetate (0·27 g.), *N*-bromosuccinimide (0·19 g.), water (7 c.c.), and ether (3 c.c.) were shaken together for 17 hours. The ethereal layer was removed, and the aqueous portion was extracted twice with ether. The combined extracts were dried (Na_2SO_4) and evaporated. The crude bromohydrin (0·35 g.) was heated with acetic acid (1 c.c.), acetic anhydride (1 c.c.), and fused sodium acetate (0·25 g.) for 24 hours on the steam-bath. The reaction mixture was cooled, shaken with water for some time, and extracted with chloroform. The extracts were washed ($NaHCO_3$ solution), dried (Na_2SO_4), and evaporated to a syrup, which partly crystallised. The solid was removed and washed with ethanol–light petroleum (b. p. 40—60°), to give hexa-acetyl sorbitol, (0·08 g.), m. p. and mixed m. p. 96—98°, $[\alpha]^{20}_{\mathrm{D}}$ +9·0° (*c*, 1·0 in chloroform).

3 : 4-*Dimethanesulphonyl* 1 : 2-5 : 6-*Diisopropylidene Mannitol*.—To a solution of methansulphonyl chloride (7·15 g.) in dry pyridine (15 c.c.), cooled in ice, was added powdered 1 : 2-5 : 6-di*iso*propylidene mannitol (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338) (6·6 g.), during *ca.* 5 minutes. After being kept at 0° overnight, the mixture was diluted with water (200 c.c.). The precipitated solid was collected, washed with water, and recrystallised from methanol to give the *dimethanesulphonate* (9·0 g.), m. p. 143—144°, $[\alpha]^{24}_{\mathrm{D}}$ −5·2 (*c*, 2·4 in chloroform) (Found: C, 39·7; H, 6·3. $C_{14}H_{26}O_{10}S_2$ requires C, 40·2; H, 6·3%).

Reactions of the 3 : 4-*Disulphonates with Sodium Iodide*.—(*a*) 3 : 4-Ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol (Brigl and Grüner, *Ber.*, 1934, **67**, 1969) (2·9 g.), sodium iodide (6·0 g.), and acetone (40 c.c.) were heated in a sealed tube for 2 hours at 80°; no reaction occurred. Heating was continued for 12 hours at 110°; iodine was then liberated, and from the cooled reaction product the theoretical amount of sodium toluene-*p*-sulphonate (1·9 g.) was removed by filtration. The filtrate was worked up as previously described, but gave only a trace of dark oil from the chloroform extracts.

(*b*) The corresponding 3 : 4-dimethanesulphonate (12·5 g.), sodium iodide (36 g.), and acetone (250 c.c.) were heated in a pressure bottle at 100° for 55 hours. The precipitated sodium methanesulphonate amounted to only 2·2 g. (23%); the dark filtrate, containing free iodine, was returned to the bottle and heated for 15 hours at 125—135°. The reaction had now gone to completion (total yield of sodium methanesulphonate, 9·5 g.), and the mixture was worked up as before. The only identifiable product from the chloroform extractions was mesityl oxide.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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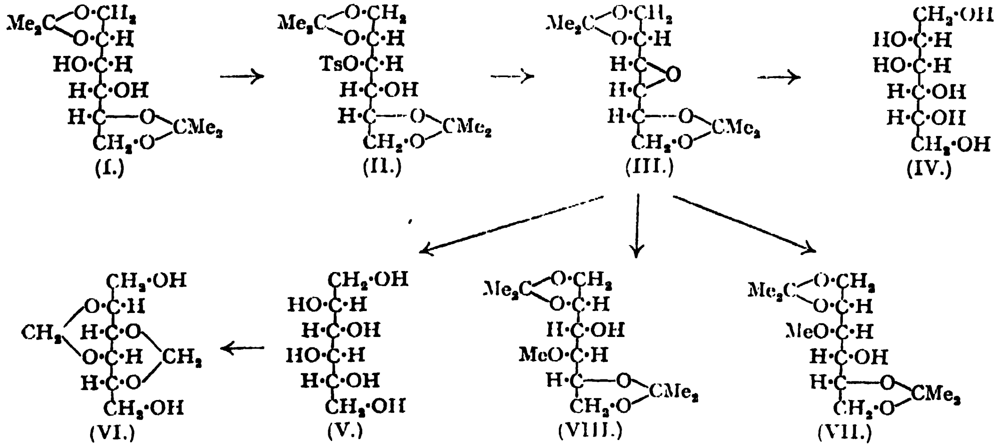
114. 1 : 2-5 : 6-*Di*iso*propylidene* 3 : 4-*Anhydro*-D-*talitol*.

By Peter Bladon and L. N. Owen.

The preparation of 1 : 2-5 : 6-*di*iso*propylidene* 3 : 4-*anhydro*-D-*talitol* from 3-*tosyl* 1 : 2-5 : 6-*di*iso*propylidene mannitol* is described. This anhydro-compound is the first non-terminal hexitol derivative of the ethylene oxide type to be obtained. Although the anhydro-ring is more stable than when it is attached to a terminal carbon atom, it is broken by acid hydrolysis, to give a mixture of D-mannitol and D-iditol, and also by treatment with alkoxides under vigorous conditions.

Derivatives of only three anhydro-hexitols of the ethylene oxide type have hitherto been described, *viz.*, 1-tosyl 2 : 4-benzylidene and 1 : 3-2 : 4-diethylidene 5 : 6-anhydrosorbitol (Vargha, *Ber.*, 1935, **68**, 1377; Vargha and Puskás, *Ber.*, 1943, **76**, 859; Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837; Wiggins, *J.*, 1946, 388); 1 : 2-3 : 4-di*iso*propylidene 5 : 6-anhydromannitol (Wiggins, *loc. cit.*); and 3 : 4-*iso*propylidene and 3 : 4-ethylidene 1 : 2-5 : 6-dianhydromannitol (Wiggins, *J.*, 1946, 384). In all these, the oxide rings engage terminal carbon atoms and are readily opened either by acid hydrolysis or by treatment with alkoxides or organic bases; the ring fission occurs usually between the oxygen atom and the terminal carbon atom, so that no change of configuration results. For example, 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol on acid hydrolysis gives only mannitol, and with sodium methoxide only 1 : 6-dimethyl 3 : 4-*iso*propylidene mannitol is obtained. The sole exception to this generalisation is provided by 1-tosyl 2 : 4-benzylidene 5 : 6-anhydrosorbitol, which on acid hydrolysis gives 1-tosyl 2 : 5-anhydro-L-iditol by Walden inversion at $C_{(5)}$ (Vargha and Puskás, *loc. cit.*).


Me₂C O·CH₂ O·C·H HO·C·H H·C·OH H·C—O CMe₂ CH₂·O
(I.)
Me₂C O·CH₂ O·C·H TsO·C·H H·C·OH H·C—O CMe₂ CH₂·O
(II.)
Me₂C O·CH₂ O·C·H H·C O H·C H·C—O CMe₂ CH₂·O
(III.)
CH₂·OH HO·C·H HO·C·H H·C·OH H·C·OH CH₂·OH
(IV.)
CH₂·OH O·C·H CH₂ H·C·O O·C·H CH₂ H·C·O CH₂·OH
(VI.)
CH₂·OH HO·C·H H·C·OH HO·C·H H·C·OH CH₂·OH
(V.)
Me₂C O·CH₂ O·C·H H·C·OH MeO·C·H H·C—O CMe₂ CH₂·O
(VIII.)
Me₂C O·CH₂ O·C·H MeO·C·H H·C·OH H·C—O CMe₂ CH₂·O
(VII.)

In connection with the synthesis of polyhydroxy-dithiols, the 5 : 6-anhydro-derivatives of mannitol and of sorbitol have been used for the preparation of the 6-allyl ethers, by effecting ring fission with sodium allyl oxide in allyl alcohol (Bladon and Owen, Part VI, *J.*, 1950, 591). As part of a possible route for the synthesis of non-terminal allyl ethers of polyhydric alcohols, a non-terminal epoxide was required, and, since anhydro-compounds of the ethylene oxide type are most conveniently prepared from tosyl compounds (cf. Peat, " Advances in Carbohydrate Chemistry," **2**, 37), attempts were made to form the monotosyl derivative (II) of 1 : 2-5 : 6-di*iso*propylidene mannitol (I). When this compound was treated with 1 mole of toluene-*p*-sulphonyl chloride in pyridine, a syrup was obtained from which 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol (Brigl and Grüner, *Ber.*, 1934, **67**, 1969) could be separated by crystallisation from methanol, and from which, on one occasion, crystalline 3-*tosyl* 1 : 2-5 : 6-*di*iso*propylidene mannitol* (II) was also obtained. Subsequent attempts to isolate this mono-derivative from the reaction mixture were unsuccessful, but such isolation proved to be unnecessary, since treatment of the crude reaction product, in chloroform, with cold methanolic sodium methoxide gave an oil, from which the ditosyl compound (unaffected by this treatment) was precipitated by light petroleum; distillation of the material soluble in this solvent then gave crystalline 1 : 2-5 : 6-*di*iso*propylidene* 3 : 4-*anhydro*-D-*talitol* (III).

The configuration allocated to this compound is in conformity with the knowledge that, in the formation of an epoxide from a tosyl compound, a Walden inversion occurs on the carbon atom carrying the sulphonyloxy-group; it was also confirmed by the following observations. Acid hydrolysis of the epoxide resulted in fission of the ring and loss of the *iso*propylidene residues, and gave a mixture of hexitols from which mannitol (IV) was isolated by crystallisation. The material in the mother-liquors, on treatment with formaldehyde and concentrated hydrochloric acid, gave a dimethylene hexitol, the properties of which agreed with those given by Hann and Hudson (*J. Amer. Chem. Soc.*, 1945, 67, 602) for 2 : 4-3 : 5-dimethylene L-iditol, except that the optical rotation was of opposite sign. Accordingly, the product is formulated as 2 : 4-3 : *5-dimethylene* D-*iditol* (VI), formed from D-iditol (V) resulting from the hydrolysis of the anhydro-compound. Acetylation of (VI) gave 1 : *6-diacetyl* 2 : 4-3 : *5-dimethylene* D-*iditol* which likewise had properties, differing only in the sign of rotation, similar to those recorded by Hann and Hudson (*loc. cit.*) for the enantiomorph. The production of both D-mannitol and D-iditol from the anhydro-compound can be explained only by assigning to it the D-talitol configuration; ring-opening thus occurs in two directions, leading (with inversion on $C_{(3)}$) to the mannitol configuration and (with inversion on $C_{(4)}$) to the iditol configuration.

1 : 2-5 : 6-Di*iso*propylidene 3 : 4-anhydro-D-talitol, the first non-terminal epoxide in the hexitol series, was noticeably more resistant than terminal epoxides to attack by alkoxides, being recovered largely unchanged after being heated under reflux with 0·2N-methanolic sodium methoxide, conditions under which terminal epoxides are readily opened (Vargha and Puskás, *loc. cit.*). With 3·5N-methanolic sodium methoxide at 100°, however, it gave a mixture of 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol (VII) and (probably) 3(or 4)-methyl 1 : 2-5 : 6-di*iso*propylidene D-iditol (VIII), from which, by acid hydrolysis, 3-methyl mannitol was obtained, identical with the compound prepared by Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, 65, 70) by reduction of 3-methyl mannose. It was not possible to isolate the 3-methyl iditol which presumably was also present.

Similarly, on being heated with sodium allyl oxide in allyl alcohol at 100°, the epoxide gave a mixture of 3-allyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol and (probably) 3-allyl 1 : 2-5 : 6-di*iso*propylidene D-iditol. Acid hydrolysis then gave a mixture of allyl hexitols from which 3-allyl D-mannitol was isolated, identical with the material obtained by direct allylation of 1 : 2-5 : 6-di*iso*propylidene mannitol (Bladon and Owen, *loc. cit.*).

EXPERIMENTAL.

3-*Tosyl* 1 : 2-5 : 6-*Diisopropylidene Mannitol.*—A solution of 1 : 2-5 : 6-di*iso*propylidene mannitol (52·4 g., 0·2 mol.) (Baer, *J. Amer. Chem. Soc.*, 1945, 67, 338) in dry pyridine (200 c.c.) was stirred vigorously and cooled during the addition of a solution of toluene-*p*-sulphonyl chloride (40 g., 0·21 mol.) in dry pyridine (100 c.c.) during 2½ hours, the temperature being kept below 2°. After the mixture had remained for 20 hours at room temperature, the greater part of the pyridine was removed by distillation under reduced pressure. The syrupy residue was taken up in chloroform (250 c.c.) and treated with crushed ice (300 g.). The chloroform layer was separated and the aqueous solution was extracted twice more with chloroform. The extracts were washed with water, dilute sulphuric acid, and finally with sodium hydrogen carbonate solution, and then dried (Na_2SO_4). The solvent was removed by distillation, leaving a syrup (66·1 g.) which was, in general, used without further treatment for the next stage. In one experiment, however, a portion (4·5 g.) of this crude monotosyl derivative was crystallised from methanol; the first crop of solid consisted of 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol, m. p. and mixed m. p. 118—119°. Treatment of the methanolic mother-liquors with water gave a solid (2·6 g.), m. p. 75—90°; this was dissolved in ethyl acetate, and the solution was dried (Na_2SO_4), concentrated to small volume, and treated with light petroleum (b. p. 60—80°) to give a solid, m. p. 98—100°. Further recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave 3-*tosyl* 1 : 2-5 : 6-*diisopropylidene mannitol*, m. p. 100°, $[\alpha]_D^{19}$ −27° (*c*, 0·9 in chloroform) (Found : C, 54·6; H, 6·6. $C_{19}H_{28}O_8S$ requires C, 54·8; H, 6·8%). Attempts to isolate this compound on other occasions were unsuccessful; furthermore, the analytically pure material decomposed after a few weeks to a viscid mass, which was acidic and contained free acetone.

1 : 2-5 : 6-*Diisopropylidene* 3 : 4-*Anhydro*-D-*talitol.*—To a solution of the crude 3-tosyl di*iso*propylidene mannitol syrup (60 g.) in chloroform (240 c.c.), cooled in ice, was added a solution of sodium (3·5 g.) in dry methanol (150 c.c.), with shaking and cooling. The sodium toluene-*p*-sulphonate first separated as a gel, which later crystallised. The mixture was left overnight at 0° and was then treated with water (500 c.c.). The chloroform layer was separated, and the aqueous portion was extracted thrice with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to a syrup (37·6 g.), which was dissolved in boiling light petroleum (b. p. 60—80°; 100 c.c.); the solid which separated on cooling was collected and extracted twice more with light petroleum. The insoluble material (15 g.) was recrystallised from methanol (100 c.c.) and gave long needles of 3 : 4-ditosyl 1 : 2-5 : 6-di*iso*propylidene mannitol (8·5 g.), m. p. 118°, $[\alpha]_D^{21}$ +7·8° (*c*, 2·5 in chloroform) (Found : C, 54·8; H, 5·9. Calc. for $C_{26}H_{34}O_{10}S_2$: C, 54·7; H, 6·0%). Brigl and Grüner (*Ber.*, 1934, 67, 1969) give m. p. 120—121°, $[\alpha]_D$ +9·3° (in chloroform).

Evaporation of the petroleum solution under reduced pressure gave a crystalline residue (25 g.) which was distilled at 80—140° (air-bath)/0·0001 mm.; the distillate (20·7 g.) solidified in the form of large plates, m. p. 49—53°. Recrystallisation from aqueous methanol gave large granular crystals of

1 : 2-5 : 6-*diïsopropylidene* 3 : 4-*anhydro*-D-*talitol*, m. p. 54—56°, $[\alpha]_D^{22}$ −16·2° (*c*, 1·5 in chloroform) (Found: C, 59·3; H, 8·1. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·3%). The overall yield of the anhydro-compound from di*iso*propylidene mannitol was 43%.

Acid Hydrolysis of 1 : 2-5 : 6-*Diïsopropylidene* 3 : 4-*Anhydro*-D-*talitol.*—The compound (4·9 g.) was heated on the steam-bath with 0·9N-sulphuric acid (5 c.c.) for 2½ hours, the liberated acetone being allowed to escape. The cooled solution was then extracted once with ether, to remove a trace of oily impurity, and treated with a slight excess of barium hydroxide solution, the excess then being neutralised with carbon dioxide. The precipitate was removed on the centrifuge and washed twice with a little water. Evaporation of the aqueous solution under reduced pressure then gave a syrup, which was evaporated several times with ethanol and then dissolved in ethanol (45 c.c.) and water (4 c.c.). This solution was filtered and concentrated to small bulk; successive treatments with small quantities of ethyl acetate then gave three crops of mannitol, m. p. 163—166°, 160—161°, and 161—163°, respectively, undepressed on admixture with authentic mannitol of m. p. 166° (iditol has m. p. 73—74°). The total yield was 1·83 g. Evaporation of the mother-liquors gave a syrup (2·0 g.), which contained iditol (see below).

2 : 4-3 : 5-*Dimethylene* D-*Iditol.*—The syrup (2·0 g.) was heated on the steam-bath with 40% aqueous formaldehyde solution (5 c.c.) and concentrated hydrochloric acid (5 c.c.) for 6 hours, and then left overnight at room temperature. The solution was filtered and evaporated on the steam-bath to a syrup, which was dissolved in a little water and again evaporated to yield a solid residue. This was dissolved in boiling water (10 c.c.), and the solution was filtered; on cooling, a crystalline solid separated, m. p. 262—265° (0·52 g.), and on further recrystallisation from water and from aqueous methanol (with charcoal) small plates of 2 : 4-3 : 5-*dimethylene* D-*iditol* were obtained, having m. p. 262—265° (decomp.), $[\alpha]_D^{22}$ −38·5° (*c*, 0·3 in water) Found: C, 46·25; H, 6·6. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%). Hann and Hudson (*loc. cit.*), for the L-form, recorded m. p. 260—262° (decomp.), $[\alpha]_D^{20}$ +39·2° in water.

The mother-liquors from the above crystallisations were re-treated with formaldehyde and hydrochloric acid, and gave a further small quantity of dimethylene D-iditol.

1 : 6-*Diacetyl* 2 : 4-3 : 5-*Dimethylene* D-*Iditol.*—2 : 4-3 : 5-Dimethylene D-iditol (0·2 g.) was dissolved in a mixture of acetic acid (0·6 c.c.) and acetic anhydride (1·4 c.c.). Concentrated sulphuric acid (0·05 c.c.) was added, and after a few minutes the reaction mixture was poured into water. The precipitated solid was recrystallised first from ethanol and finally from water, and gave needles (0·1 g.) of the *diacetyl* derivative, m. p. 220—221°, $[\alpha]_D^{20}$ +4·8° (*c*, 0·9 in chloroform) (Found: C, 49·7; H, 6·1. $C_{12}H_{18}O_8$ requires C, 49·65; H, 6·25%). Hann and Hudson (*loc. cit.*), for the L-enantiomorph, give m. p. 219—220°, $[\alpha]_D^{20}$ −3·9° in chloroform.

Reaction of 1 : 2-5 : 6-*Diïsopropylidene* 3 : 4-*Anhydro*-D-*talitol with Sodium Methoxide.*—Heating of the anhydro-compound with 0·2N-methanolic sodium methoxide under reflux for periods up to 15 hours resulted in no significant change in optical rotation, and the material was recovered almost quantitatively from the solution. With 2N-methanolic sodium methoxide in a sealed tube at 100°, a change in $[\alpha]_D$ from −23·2° (initial) to +5·1° (6 hours) was observed.

The anhydro-compound (5 g.) was therefore dissolved in 3·5N-methanolic sodium methoxide (35 c.c.; and the solution was heated in a small autoclave at 100—105° for 20 hours. The cooled product was diluted with water, neutralised with carbon dioxide, and concentrated under reduced pressure to remove most of the methanol. The aqueous solution was then extracted with ether (5 × 50 c.c.), the extracts were dried (Na_2SO_4), and the solvent was evaporated. Distillation of the residual syrup (5·0 g.) gave a colourless liquid, probably a mixture of 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol and 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-iditol, b. p. 96°/0·003 mm., n_D^{19} 1·4530, $[\alpha]_D^{21}$ +6·8° (*c*, 4 in chloroform) (Found: C, 56·5; H, 8·6. Calc. for $C_{13}H_{24}O_6$: C, 56·5; H, 8·8%). A di*iso*propylidene compound of uncertain structure from 3-methyl mannitol, prepared by Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 70), had m. p. 57—58°, $[\alpha]_D^{20}$ +9·0° (in alcohol).

3-*Methyl Mannitol.*—The above mixture was hydrolysed by being heated with 0·45N-sulphuric acid (10 c.c.) for 7 hours, the acetone being removed from the liquid by the passage of a slow stream of nitrogen. The solution was extracted once with ether, to remove oily impurities, and it was then heated to *ca.* 80° and treated with a slight excess of barium hydroxide solution, the excess then being removed with carbon dioxide. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to a syrup, which was dried by evaporation several times with ethanol. It was then dissolved in hot ethanol (20 c.c.) and filtered from a small amount of insoluble matter. Evaporation then gave a syrup (2·7 g.; calc. yield of methyl hexitol, 2·8 g.) which on treatment with ethanol–ethyl acetate gave a precipitate of 3-methyl mannitol monohydrate (1·25 g., 45%), m. p. 85—86°. Haskins, Hann, and Hudson (*loc. cit.*) give m. p. 86—87°. Crystallisation from dry ethanol gave the anhydrous 3-methyl mannitol, m. p. 132—133°, $[\alpha]_D^{20}$ +16·5° (*c*, 2 in water). Haskins *et al.* (*ibid.*) give m. p. 133—134°, $[\alpha]_D^{20}$ +16·7° (*c*, 2 in water).

Evaporation of the mother-liquors from the initial precipitation of 3-methyl mannitol gave a syrup (1·4 g.) which could not be induced to crystallise, and presumably contained 3-methyl iditol.

3-*Allyl* D-*Mannitol.*—When 3 : 4-anhydro-D-talitol was heated with 0·1N-sodium allyl oxide in allyl alcohol for 5½ hours under reflux, the greater part of the material was recovered unchanged. A solution of the anhydro-compound (6·1 g.) in dry allyl alcohol (50 c.c.) containing sodium (5 g.; *i.e.*, a 4N-solution) was heated under an air reflux condenser for 17 hours, during which time the solution became more concentrated owing to loss of solvent. The syrupy product was treated with water (100 c.c.) and steam-distilled to remove allyl alcohol. The alkali was neutralised with carbon dioxide, and the solution was extracted with ether (4 × 60 c.c.). The dried (Na_2SO_4) extracts were then evaporated and the residual oil was distilled to give a mixture (7·0 g., 94%) of 3-allyl 1 : 2-5 : 6-di*iso*propylidene D-mannitol and 3-allyl 1 : 2-5 : 6-di*iso*propylidene D-iditol, b. p. 94—97°/0·001 mm., n_D^{20} 1·4634, $[\alpha]_D^{23}$ +4·1° (*c*, 2 in chloroform) (Found: C, 59·85; H, 8·4. Calc. for $C_{15}H_{26}O_6$: C, 59·6; H, 8·7%). This mixture was hydrolysed in a similar way to that used for the corresponding methyl compounds and gave 3-allyl D-mannitol (1·6 g., 30%), m. p. and mixed m. p. 117—118°, $[\alpha]_D^{23}$ +17·7° (*c*, 1 in water) (cf. Bladon and

Owen, *J.*, 1950, 591). Evaporation of the mother-liquors gave a syrup (1·75 g.) from which no crystalline material could be obtained.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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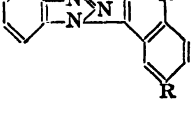
115. *Attempts to Find New Antimalarials. Part XXIX. The Synthesis of Various Derivatives of 2 : 3-Benz-γ-carboline.*

By WILLIAM O. KERMACK and (MRS.) NORA E. STOREY.

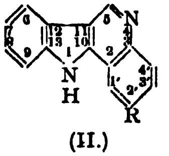
The Graebe–Ullmann method has been used to synthesise 2 : 3-benz-γ-carboline (II; R = H) and a number of its derivatives. Treatment of 2 : 3-benz-γ-carboline with 2-diethylaminoethyl chloride in nitrobenzene yields 4-2″-*diethylaminoethyl*-2 : 3-*benz*-γ-*isocarboline* (X), whilst in toluene in presence of sodamide the product of the reaction is 1-2″-*diethylaminoethyl*-2 : 3-*benz*-γ-*carboline* (IX). The structure of (IX) has been confirmed by the synthesis of its dimethiodide (XII) from 4-*methyl*-2 : 3-*benz*-γ-isocarboline (XI) and 2-diethylaminoethyl chloride, followed by treatment of the resulting 4-methyl-1-2″-diethylaminoethyl-2 : 3-benz-γ-carbolinium chloride, first with potassium iodide and then with methyl iodide. Two by-products isolated by Schofield and Simpson in the preparation of ethyl 4-hydroxyquinoline-3-carboxylate from aniline and ethyl ethoxymethylenemalonate have been identified.

A NUMBER of derivatives of 2 : 3-benz-γ-carboline containing a methyl group in position 5 have been synthesized by Kermack and Smith (*J.*, 1930, 1999). Clemo and Perkin (*ibid.*, 1924, 125, 1608) treated the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-4-quinolone with 20% sulphuric acid and instead of the expected 4 : 5-dihydro-2 : 3-benz-γ-carboline, $C_{15}H_{12}N_2$, isolated a compound, $C_{15}H_{10}N_2$, m.p. >320°, which they assumed to be 2 : 3-benz-γ-carboline (indolo-3′ : 2′-3 : 4-quinoline) itself. During investigations on the constitution of indigo-yellow, de Diesbach, de Bie, and Rubli (*Helv. Chim. Acta*, 1934, 17, 113) isolated a degradation product, m. p. 332°, which they considered on the basis of oxidation experiments to be 2 : 3-benz-γ-carboline. It seemed desirable to synthesise this base by an unambiguous method and at the same time to prepare a number of derivatives carrying basic side chains in order that they might be subjected to biological tests.

The method employed was a modification of the Graebe–Ullmann carbazole synthesis used by Kermack and Smith in their synthesis of the 5-methyl derivatives of 2 : 3-benz-γ-carboline (*loc. cit.*). Thus 4-chloroquinoline was condensed with *o*-phenylenediamine, and the resulting 4-*o*-*aminoanilinoquinoline* treated with nitrous acid to yield the *benztriazole* derivative (I; R = H). When heated in syrupy phosphoric acid this compound lost nitrogen and underwent the Graebe–Ullmann reaction to yield 2 : 3-benz-γ-carboline (II; R = H). Here it is assumed that cyclization occurs so as to involve position 3 of the quinoline nucleus, although it might occur at position 5 to yield the isomeric compound (III). The latter course is excluded not only by the properties of the product, but also by the experiments in the 5-methyl series (Kermack and Smith, *loc. cit.*).



(I.)



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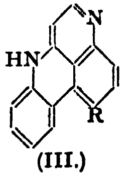

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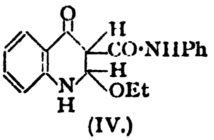

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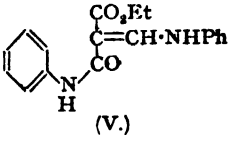

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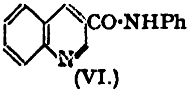

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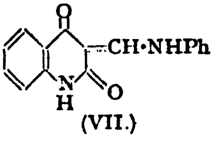


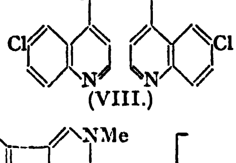
(VII.)

4-Chloroquinoline was prepared from aniline and ethyl ethoxymethylenemalonate (cf. Schofield and Simpson, *J.*, 1946, 1033, and Price and Roberts, *J. Amer. Chem. Soc.*, 1946, 68, 1204). When somewhat impure ethyl ethoxymethylenemalonate was employed cyclization of the crude intermediate ethyl anilinomethylenemalonate in liquid paraffin at 250° yielded three crystalline products. One of these was ethyl 4-hydroxyquinoline-3-carboxylate; the other two melted at 118° and 318° respectively and were evidently identical with Schofield and Simpson's by-products, $C_{18}H_{18}O_3N_2$ and $C_{16}H_{12}O_2N_2$ respectively (*loc. cit.*). Schofield and Simpson suggested for the lower-melting compound formula (IV) or (V) and for the higher-melting compound the formula (VI) or (VII), the last compound being formed from (V) by the loss of a molecule of ethanol. The following observations decide the constitution of these two products.

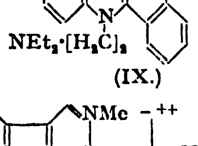
The compound, m. p. 118°, when heated in diphenyl was converted into the compound, m. p. 318°, with loss of ethanol. The compound, m. p. 318°, when boiled with acid yielded 4-hydroxyquinoline-3-carboxylic acid and also a diazotisable amine, presumably aniline. This strongly suggests that the compound is 4-*hydroxyquinoline*-3-*carboxyanilide* (VI), which is confirmed by its synthesis from equimolecular amounts of ethyl 4-hydroxyquinoline-3-carboxylate and aniline. As (VI) is formed from the lower-melting compound with the loss of a molecule of alcohol, it appears very probable that the latter has the formula (V) and not (IV), which is confirmed by its synthesis from equimolecular amounts of ethyl anilinomethylenemalonate and aniline.

In contrast to Schofield and Simpson (whose product did not crystallise) and Price and Roberts (who obtained a product which set to a crystalline mass between −12° and −15°) we found that *p*-anisidine and ethyl ethoxymethylenemalonate, when heated on a steam-bath, yielded a crystalline compound, m. p. 38—40°; its analyses were in accord with its formulation as *ethyl* p-*anisidinomethylenemalonate* and it was converted into 4-chloro-6-methoxyquinoline by the series of reactions described by Price and Roberts.

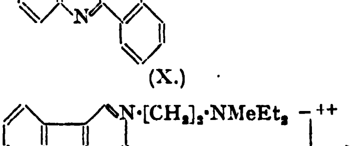
From 4-chloro-6-methoxyquinoline and *o*-phenylenediamine, 4-o-*aminoanilino*-6-*methoxyquinoline* was obtained, which with nitrous acid yielded the *benztriazole* derivative (I; R = OMe). This, when heated in syrupy phosphoric acid, afforded 2′-*methoxy*-2 : 3-*benz*-γ-*carboline* (II; R = OMe). From 4 : 6-dichloroquinoline by an analogous series of reactions, there was obtained 2′-*chloro*-2 : 3-*benz*-γ-*carboline* (II; R = Cl). On one occasion in the preparation of 2′-methoxy-2 : 3-benz-γ-carboline, 6-*methoxy*-4-(*benztriazol*-1-*yl*)*quinoline*, when heated in syrupy phosphoric acid, yielded 4-*anilino*-6-*methoxyquinoline*, the identity of which was confirmed by its synthesis from 4-chloro-6-methoxyquinoline and aniline. The special conditions responsible for the reaction taking this abnormal course were not ascertained; it would seem that some reducing agent must inadvertently have been present. A by-product isolated on one occasion from the reaction between 4 : 6-dichloroquinoline and *o*-phenylenediamine proved to be NN′-*di*-(6-*chloro*-4-*quinolyl*)-o-*phenylenediamine* (VIII), the structure of which was confirmed by its synthesis from 6-*chloro*-4-o-*aminoanilinoquinoline* and 4 : 6-dichloroquinoline. (VIII) yielded a *dimethiodide* when boiled in nitrobenzene with excess of methyl sulphate and then treated with potassium iodide.



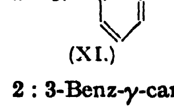
(VIII.)



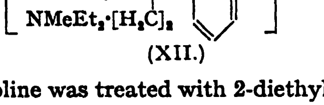
(IX.)



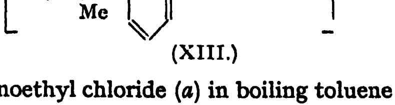
(X.)



(XI.)



(XII.)



(XIII.)

2 : 3-Benz-γ-carboline was treated with 2-diethylaminoethyl chloride (*a*) in boiling toluene in presence of sodamide (cf. Dewar, *J.*, 1944, 619) and (*b*) in nitrobenzene at 100°. Two products were obtained: method (*a*) yielded a base, m. p. 103—104°, which was considered to be 1-2″-*diethylaminoethyl*-2 : 3-*benz*-γ-*carboline* (IX), whilst the product, m. p. 84—86°, obtained by method (*b*) was probably 4-2″-*diethylaminoethyl*-2 : 3-*benz*-γ-iso*carboline dihydrate* (X). The latter compound, even after prolonged drying, contained a molecule of water, so that it may clearly be either the carbolinium hydroxide (in its ionic form or as the pseudo-base), or the monohydrate of the anhydronium base; it is relatively soluble in both benzene and light petroleum, and readily

forms a dimethiodide, one of the methyl groups of which is undoubtedly attached at $N_{(1)}$ (see below); it thus behaves as the anhydronium base rather than as the quaternary hydroxide, and this conclusion is confirmed by the fact that the analogous compound derived from 2′-chloro-2 : 3-benz-γ-carboline, when dried, forms first a compound of similar composition to that above, and then yields the anhydrous anhydronium base. However, the distinction between a hydrated anhydronium base and a quaternary hydroxide is not sharp, as the hydrated anhydronium base with a hydrogen atom co-ordinated at $N_{(1)}$ is scarcely distinguishable from the quaternary hydroxide.

When treated with excess of methyl iodide and nitrobenzene the bases (IX) and (X) yielded dimethiodides, m.p. 276—278° and 263—264° respectively. The dimethiodide, m. p. 276—278°, was also prepared as follows: from the *methiodide* of 2 : 3-benz-γ-carboline, the anhydronium base, 4-*methyl*-2 : 3-*benz-γ-iso*carboline (XI), was obtained by treatment with alkali; when this compound was warmed in nitrobenzene with 2-diethylaminoethyl chloride and the product treated with potassium iodide, a compound, m. p. 225°, was isolated which, on treatment with methyl iodide, yielded a compound, m. p. 276—278°, identical with the dimethiodide in question. In this second method of synthesis one methyl group is certainly located at $N_{(4)}$; it has been amply proved that, when alkyl*iso*carbolines are treated with alkyl halides, the second alkyl group becomes attached to $N_{(1)}$. It follows that the diethylaminoethyl group is here attached to $N_{(1)}$, so that the dimethiodide in question must have the structure (XII). This in turn proves that the product obtained by method (*a*) must have the constitution (IX), and the structure (X) of the product obtained by method (*b*) necessarily follows; the dimethiodide of (X) has presumably the structure (XIII).

Similarly, from 2′-chloro-2 : 3-benz-γ-carboline and 2-diethylaminoethyl chloride two compounds were obtained: under conditions (*a*) 2′-*chloro*-1-2″-*diethylaminoethyl*-2 : 3-*benz-γ-carboline*, and under conditions (*b*) 2′-*chloro*-4-2″-*diethylaminoethyl*-2 : 3-*benz-γ-iso*carboline. From 2′-*methoxy*-2 : 3-*benz-γ-carboline* conditions (*b*) afforded 2′-methoxy-4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline, isolated as the *dinitrobenzoate*, but it was not possible to isolate a crystalline compound from the products obtained under conditions (*a*). A by-product encountered in the experiments carried out under conditions (*b*) was 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride, formed by the interaction of two molecules of 2-diethylaminoethyl chloride. It was identified as its di-iodide, previously prepared by Gough and King (*J.*, 1928, 2430).

EXPERIMENTAL.

4-*Hydroxyquinoline-3-carboxyanilide*.—Ethyl 4-hydroxyquinoline-3-carboxylate (1 g.) was refluxed with aniline (1 g.) for 5 hours. On cooling the solution deposited shining white plates of the *anilide*, m. p. 316—318° (from acetic acid) (Found: C, 72·3; H, 4·6; N, 10·85. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·7; N, 10·6%).

Ethyl β-Anilino-α-phenylcarbamylacrylate.—Equimolecular amounts of ethyl anilinomethylenemalonate and aniline were heated together at 100° for 1 hour; the *product*, recrystallised from light petroleum, had m. p. 118° (Found: C, 69·4; H, 5·9; N, 9·3. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%).

Conversion of Ethyl β-Anilino-α-phenylcarbamylacrylate into 4-Hydroxyquinoline-3-carboxyanilide.—Ethyl β-anilino-α-phenylcarbamylacrylate (0·5 g.) was heated in boiling diphenyl under reflux for 30 minutes. The diphenyl was extracted with ether to leave a solid residue, m. p. 315°. After crystallisation from glacial acetic acid, this product showed no depression in m. p. when mixed with a sample of 4-hydroxyquinoline-3-carboxyanilide.

4-o-*Aminoanilinoquinoline*.—4-Chloroquinoline (3·2 g.) (cf. Price and Roberts, *loc. cit.*) and *o*-phenylenediamine (2·1 g.) were heated together at 140° at 20—30 mm. After 10—20 minutes a brisk reaction occurred, and the solution set to a brittle resin. The solid was extracted with boiling N-hydrochloric acid and the solution filtered. The filtrate on cooling deposited the hydrochloride as greyish-white crystals, m. p. 285—290°. The *base* precipitated by alkali from an aqueous solution of this salt was recrystallised from a mixture of benzene and light petroleum (b. p. 40—60°) and formed buff-coloured prisms, m. p. 165—166° (3·5 g., 76%) (Found: C, 76·4; H, 5·4; N, 17·4. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·8%).

4-(*Benztriazol*-1-*yl*)*quinoline*.—4-*o*-Aminoanilinoquinoline (3 g.), dissolved in N-hydrochloric acid (500 c.c.) and cooled to 5°, was treated with a solution of sodium nitrite (0·8 g.) in water (10 c.c.) until an excess of nitrite was present. The voluminous white precipitate was dissolved in boiling water, and 4-(*benztriazol*-1-*yl*)*quinoline*, precipitated by the addition of alkali, was recrystallised from ethanol; it formed slender white prisms, m. p. 132—133° (2·2 g., 70%) (Found: C, 73·0; H, 4·2; N, 23·0. $C_{15}H_{10}N_4$ requires C, 73·2; H, 4·1; N, 22·8%).

2 : 3-*Benz-γ-carboline*.—4-(Benztriazol-1-yl)quinoline (10 g.) was heated in syrupy phosphoric acid (15 c.c.) until the evolution of nitrogen ceased. The greyish-white precipitate which separated from the cool solution on dilution and basification was filtered off, washed, and recrystallised from aqueous methanol; it formed irregular colourless prisms, m. p. 342° with sublimation (7 g., 77%) (Found: C, 82·3; H, 4·9; N, 12·55. Calc. for $C_{15}H_{10}N_2$: C, 82·55; H, 4·6; N, 12·8%). This compound is insoluble in benzene or ether, sparingly soluble in ethanol, and more soluble in methanol or pyridine. It dissolves readily in hot dilute hydrochloric acid to give a clear solution which on cooling deposits white

crystals of the hydrochloride, and in hot concentrated nitric acid to yield a yellow nitrate (cf. Clemo and Perkin, and de Diesbach, de Bie, and Rubli, *locc. cit.*). The base exhibits a violet fluorescence under the arc light in most solvents, but not in concentrated sulphuric acid, though the crude product showed a marked fluorescence in the cold (cf. Clemo and Perkin, *loc. cit.*).

From 2 : 3-benz-γ-carboline and excess of methyl iodide in nitrobenzene, after 2 hours on the steam-bath, needle-shaped crystals of the *methiodide* separated. The product, recrystallised from methanol containing a trace of sodium thiosulphate, had m. p. 297° (0·2 g., 72%) (Found: C, 53·4; H, 3·4; N, 7·5. $C_{16}H_{13}N_2I$ requires C, 53·3; H, 3·6; N, 7·8%).

When a trace of iodine dissolved in ethanol is added to the alcoholic solution of this methiodide, a dark red colour immediately develops. The crystals of the methiodide prepared in the absence of thiosulphate also tend to develop a reddish colour which deepens to black on storage. This colour which may be discharged by sodium thiosulphate is apparently due to the action of traces of iodine in the salt or in the crystals [cf. Kermack, Smith, and Spragg, *Proc. Roy. Soc.* (*Edin.*), 1929—1930, **50**, 243].

4-Methyl-2 : 3-benz-γ-isocarboline.—An aqueous solution of the above methiodide was rendered alkaline with aqueous ammonia, and the yellow solid which separated was recrystallised from dry benzene, giving yellow prisms of the *monohydrate*, m. p. 195° (Found: C, 76·75; H, 5·5. $C_{16}H_{12}N_2,H_2O$ requires C, 76·8; H, 5·6%). The anhydrous *base*, obtained by drying the monohydrate *in vacuo* at 80° over phosphoric oxide for 4 hours, had m. p. 195° (Found: C, 82·8; H, 5·0; N, 11·7. $C_{16}H_{12}N_2$ requires C, 82·75; H, 5·2; N, 12·1%).

4-2''-Diethylaminoethyl-2 : 3-benz-γ-isocarboline.—2 : 3-Benz-γ-carboline (0·54 g.) and 2-diethylaminoethyl chloride (0·5 g.) in nitrobenzene (100 c.c.) were heated at 100° under reflux for 9 hours and set aside at room temperature overnight. The solution was filtered from some 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride and diluted with light petroleum (b. p. 100—120°) to yield a brown precipitate which was filtered off. The aqueous solution of the product was basified with aqueous ammonia to give a yellow precipitate which, recrystallised from aqueous ethanol, had m. p. 84—86°. When dried in a vacuum over calcium chloride, the yellow needles changed to a highly viscous liquid. When an analytical specimen of the crystals was dried over phosphoric oxide at 80° in a vacuum, the loss of weight was 5·07%. The resulting viscous liquid gave the following analytical values: Found: C, 74·3; H, 7·35; N, 12·2% ($C_{21}H_{23}N_3,1\frac{1}{2}H_2O$ requires C, 74·2; H, 7·5; N, 12·4%). It thus appears that the liquid is the monohydrate of the expected base and that the crystals, m. p. 84—86°, are a *dihydrate* (Required: $C_{21}H_{23}N_3,2H_2O \longrightarrow C_{21}H_{23}N_3,H_2O$, loss 5·09%).

Dimethiodide of 4-2''-Diethylaminoethyl-2 : 3-benz-γ-isocarboline.—From 4-2''-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline dihydrate (0·53 g.) and methyl iodide (0·24 g.) in nitrobenzene (10 c.c.), heated under reflux at 60° (for 30 minutes), needle-shaped crystals of a *dimethiodide* separated almost immediately. These were filtered off, washed with ether, and crystallised from boiling water, forming white feathery needles, m. p. 263—264° (Found: C, 45·75; H, 4·65; N, 6·6. $C_{21}H_{23}N_3,2CH_3I$ requires C, 45·9; H, 4·8; N, 6·9%). An aqueous solution of the salt gives no precipitate with aqueous ammonia or sodium hydroxide, indicating that an anhydronium base is not formed.

1-2''-Diethylaminoethyl-2 : 3-benz-γ-carboline.—2 : 3-Benz-γ-carboline (1·09 g.), 2-diethylaminoethyl chloride (1·01 g.), finely powdered sodamide (1·95 g.), and toluene (10 c.c.) were heated on an oil-bath at 70° for 30 minutes and then at 115° for 30 minutes, and finally refluxed at 110° for 4 hours. To the cold mixture, water was added and a small amount of insoluble 2 : 3-benz-γ-carboline removed by filtration. The toluene layer was separated and extracted with dilute acetic acid (5%). The acid extracts were basified with aqueous ammonia, and the resulting oily precipitate extracted with ether. After drying (K_2CO_3) and reduction of volume, fine crystals of the *1-2''-diethylaminoethyl* derivative separated; recrystallised from aqueous ethanol, this had m. p. 103—104° (0·96 g., 60%) (Found: C, 79·6; H, 7·1; N, 13·2. $C_{21}H_{23}N_3$ requires C, 79·5; H, 7·25; N, 13·25%).

Dimethiodide of 1-2''-Diethylaminoethyl-2 : 3-benz-γ-carboline.—The preceding base (0·5 g.), methyl iodide (0·3 g.), and nitrobenzene (10 c.c.) were heated together at 60° for 30 minutes; the white solid was washed with ether and recrystallised from methanol; this *dimethiodide* formed prisms, m. p. 276—278° (Found: C, 45·6; H, 5·1; N, 6·4. $C_{21}H_{23}N_3,2CH_3I$ requires C, 45·9; H, 4·8; N, 6·9%). Addition of aqueous ammonia or sodium hydroxide to its aqueous solution gave no precipitate.

Dimethiodide of 1-2''-Diethylaminoethyl-2 : 3-benz-γ-carboline from 4-Methyl-2 : 3-benz-γ-isocarboline.—4-Methyl-2 : 3-benz-γ-*iso*carboline (0·5 g.) and excess of 2-diethylaminoethyl chloride were heated in nitrobenzene (20 c.c.) for 6 hours under reflux and set aside at room temperature overnight. The cooled solution was filtered to remove some 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride and then diluted with light petroleum (b. p. 80—100°). The crystalline material which separated was washed with ether and dissolved in the minimum amount of water. This aqueous solution, treated with a saturated solution of potassium iodide, yielded a white precipitate which, recrystallised from ethanol, had m. p. 225°. This compound 4-methyl-1-2''-diethylaminoethyl-2 : 3-benz-γ-carbolinium iodide was treated with methyl iodide in nitrobenzene at 100°, and yielded 1-2''-diethylaminoethyl-2 : 3-benz-γ-carboline dimethiodide (m. p. 276—278°), identical (mixed m. p.) with the compound prepared by the previous method.

Ethyl p-*Anisidinomethylenemalonate.*—The oil obtained by heating *p*-anisidine (31 g.) and ethyl ethoxymethylenemalonate (54 g.) for 45 minutes on the steam-bath was freed from alcohol and triturated with light petroleum. On long storage the oil solidified and, although difficult to purify, eventually recrystallised from light petroleum (b. p. 80—100°) in large irregular prisms, m. p. 38—40° (Found: C, 61·1; H, 6·2; N, 4·9. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·8%).

4-o-*Aminoanilino-6-methoxyquinoline.*—When 4-chloro-6-methoxyquinoline (cf. Price and Roberts, *loc. cit.*) (3·9 g.) and *o*-phenylenediamine (2·16 g.) were heated together at 140° under reduced pressure a brisk reaction took place and the mixture solidified. The solid was extracted with boiling water; the hot solution was filtered and basified with aqueous ammonia; recrystallised from benzene, the *compound* formed colourless rectangular plates, m. p. 192° (Found: C, 72·3; H, 5·5; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·85%).

6-Methoxy-4-(benztriazol-1-yl)quinoline.—To a solution of the preceding base (3·5 g.) in N-hydrochloric acid (100 c.c.), a solution of sodium nitrite (1·15 g. in 5 c.c. of water) was added until a slight excess was present. The solution was set aside for 2 hours at room temperature, after which the precipitate of hydrochloride was filtered off. The *base* was precipitated from the hot aqueous solution of the hydrochloride by aqueous ammonia and, recrystallised from light petroleum (b. p. 80—100°), had m. p. 129—130° (Found : C, 70·2; H, 4·2; N, 20·5. $C_{16}H_{12}ON_4$ requires C, 69·6; H, 4·3; N, 20·3%).

2′-Methoxy-2 : 3-benz-γ-carboline.—6-Methoxy-4-(benztriazol-1-yl)quinoline (5 g.) was heated in syrupy phosphoric acid until the evolution of nitrogen ceased. The resulting reddish-brown solution was poured into a large volume of water, and aqueous ammonia added to precipitate a yellow gelatinous solid which was dried and purified through its *dihydrochloride*, m. p. 310° (Found : C, 57·5; H, 4·8; $C_{16}H_{12}ON_2,2HCl,0{\cdot}75H_2O$ requires C, 57·4; H, 4·65%). The *base*, regenerated from its hydrochloride and recrystallised from pyridine, had m. p. 315° (Found : C, 77·0; H, 4·8; N, 11·1. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

In one experiment the product of this reaction proved to be *4-anilino-6-methoxyquinoline* (Found : C, 76·4; H, 5·8. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%), which did not depress the m. p. of a specimen prepared as described below.

4-Anilino-6-methoxyquinoline.—Aniline (0·5 g.) and 4-chloro-6-methoxyquinoline (1 g.) were heated together at 100° in the presence of a trace of copper bronze for 3 hours. After cooling, the melt was dissolved in dilute hydrochloric acid from which 4-anilino-6-methoxyquinoline was precipitated by aqueous ammonia. Recrystallised from ethanol, it formed pale yellow prisms, m. p. 220° (Found : C, 76·5; H, 5·4; N, 10·9. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

*2′-Methoxy-4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline.*—2′-Methoxy-2 : 3-benz-γ-carboline (0·5 g.) and 2-diethylaminoethyl chloride in nitrobenzene were heated at 100° for 6 hours. The precipitate obtained on dilution of the cold solution with light petroleum was dissolved in water and basified with aqueous sodium hydroxide, and the resulting yellow oil extracted with ether. The ethereal extract was dried (Na_2SO_4), and the solvent removed, leaving a yellow oil which did not crystallise. The *bis-3 : 5-dinitrobenzoate* of the compound, recrystallised from ethanol, formed white prisms, m. p. 268° (Found : C, 55·7; H, 4·0; N, 12·3. $C_{22}H_{25}ON_3,2C_7H_4O_6N_2$ requires C, 56·0; H, 4·3; N, 12·7%).

*6-Chloro-4-*o*-aminoanilinoquinoline.*—4 : 6-Dichloroquinoline (9·9 g.) and *o*-phenylenediamine (5·4 g.) were heated under the conditions used for the methoxy-derivative. No reaction took place, but in the presence of a trace of copper bronze reaction occurred. The product was worked up as described for the 6-methoxy-compound; the *base*, recrystallised from light petroleum, formed irregular plates, m. p. 186—187° (Found : C, 66·8; H, 4·35; N, 15·3. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·45; N, 15·6%).

NN′-*Di-(6-chloro-4-quinolyl)-*o*-phenylenediamine.*—6-Chloro-4-*o*-aminophenylaminoquinoline (0·54 g.) and 4 : 6-dichloroquinoline (0·4 g.) were heated together under reduced pressure at 140° for 30 minutes in the presence of copper. The product was extracted with dilute hydrochloric acid (5%), and the solution basified, to yield a white precipitate of NN′-*di-(6-chloro-4-quinolyl)-*o*-phenylenediamine*; recrystallised from nitrobenzene, this formed white needles, m. p. 342—344° (Found : C, 67·2; H, 3·5; N, 12·75. $C_{24}H_{16}N_4Cl_2$ requires C, 66·8; H, 3·7; N, 13·0%). The compound was also occasionally obtained as a by-product (highly insoluble in ethanol) in the preparation of 6-chloro-4-*o*-aminoanilinoquinoline.

A solution of this pentacyclic compound (0·55 g.) in nitrobenzene was treated with methyl sulphate (1 g.) at 130° for 2 hours under reflux. When the product was set aside at room temperature a dark red oil separated which was extracted several times with water; the combined aqueous extracts were concentrated to small volume. Addition of a saturated solution of potassium iodide yielded a yellow precipitate of the *dimethiodide*, m. p. 330—332° (from water) (Found : C, 41·4; H, 3·2. $C_{24}H_{16}N_4Cl_2,2CH_3I,2H_2O$ requires C, 41·6; H, 3·5%). The aqueous solution, basified with concentrated sodium hydroxide solution, gave an orange precipitate.

6-Chloro-4-(benztriazol-1-yl)quinoline.—A solution of 6-chloro-4-*o*-aminoanilinoquinoline (6·7 g.) in N-hydrochloric acid at 100° was treated with sodium nitrite as for the methoxy-analogue. After 2 hours' storage at room temperature, the white gelatinous precipitate of the hydrochloride was filtered off, and the *base* regenerated and recrystallised from ethanol; it yielded long white needles, m. p. 185—186° (Found : C, 64·1; H, 2·9; N, 19·7. $C_{15}H_9N_4Cl$ requires C, 64·2; H, 3·2; N, 19·9%).

2′-Chloro-2 : 3-benz-γ-carboline.—6-Chloro-4-(benztriazol-1-yl)quinoline (2 g.) was heated in boiling syrupy phosphoric acid (10 c.c.) until evolution of nitrogen ceased. *2′-Chloro-2 : 3-benz-γ-carboline*, obtained by basification of the diluted solution with aqueous ammonia, crystallised from pyridine in small white needles, subliming, without melting, at >360° (Found : C, 71·4; H, 3·4; N, 10·9. $C_{15}H_9N_2Cl$ requires C, 71·3; H, 3·6; N, 11·1%).

*2′-Chloro-4-methyl-2 : 3-benz-γ-*iso*carboline.*—From 2′-chloro-2 : 3-benz-γ-carboline (0·5 g.) and an excess of methyl iodide in nitrobenzene at 100°, a crystalline methiodide separated which, recrystallised from water, melted at 225°. An aqueous solution of this methiodide was basified with sodium hydroxide, to yield a yellow base which after being washed and dried was recrystallised from benzene. Dried in a vacuum at 80° for 4 hours over P_2O_5, *15-chloro-4-methyl-2 : 3-benz-γ-*iso*carboline* melted at 245° (Found : C, 67·3; H, 4·3. $C_{16}H_{11}N_2Cl,H_2O$ requires C, 67·5; H, 4·55%).

*2′-Chloro-4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline.*—A solution of 2′-chloro-2 : 3-benz-γ-carboline (0·25 g.) in nitrobenzene (50 c.c.) was heated with 2-diethylaminoethyl chloride (0·2 g.) for 9 hours. The precipitate which formed on cooling and storage overnight at room temperature was separated, dissolved in water, and treated with aqueous ammonia hydroxide. The *base*, thus formed, was a yellow solid, which, when recrystallised from ethanol, softened at 40° and melted at 69—71°. After drying in a vacuum over potassium hydroxide and recrystallisation from dry light petroleum (b. p. 60—80°) the product melted at 125—126° (Found : C, 71·4; H, 5·9; N, 11·8. $C_{21}H_{22}N_3Cl$ requires C, 71·7; H, 6·3; N, 11·95%).

2′-Chloro-1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline.—2-Diethylaminoethyl chloride (0·14 g.), 2′-chloro-2 : 3-benz-γ-carboline (0·25 g.), and finely ground sodamide (0·03 g.) in toluene (10 c.c.) were heated at 70° for 30 minutes and then at 115° for a further 30 minutes, and refluxed at 110° for 4 hours. After the mixture had been cooled water was added, the insoluble material removed by filtration, and the toluene layer separated and extracted with 5% acetic acid, from which the base was precipitated by aqueous ammonia. The ethereal solution of the *base* was dried (K_2CO_3) and the solvent removed; the residue, recrystallised from aqueous ethanol, had m. p. 114—115° (Found: C, 71·3; H, 5·95; N, 11·6. $C_{21}H_{22}N_3Cl$ requires C, 71·7; H, 6·3; N, 11·95%). This base is a white crystalline solid and depresses the m. p. of 2′-chloro-4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline (m. p. 125—126°) described above.

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Research Laboratory,
Royal College of Physicians, Edinburgh.

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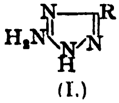
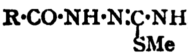
116. *Compounds related to Thiosemicarbazide. Part IV. 5-Amino-3-phenyl-1 : 2 : 4-triazoles.*

By Eric Hoggarth.

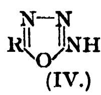
1-Benzoyl-*S*-methyl*iso*thiosemicarbazides (Part III) are cyclised by boiling with alcoholic solutions of organic bases to give a mixture of the 2-amino-5-phenyl-1 : 3 : 4-oxadiazole and 5-methylthio-3-phenyl-1 : 2 : 4-triazole. Piperidine differs from the other amines examined in giving also some of the 5-amino-3-phenyl-1 : 2 : 4-triazole. A new route to the amino-triazoles has been found in the reaction of *S*-methyl*iso*thiourea with benzhydrazides, followed by cyclisation of the resultant benzamidoguanidines.

According to Benack (Dissert., Munich, 1896, quoted in "Beilstein," First Suppl. Vol., 26, 45) 5-amino-3-phenyl-1 : 2 : 4-triazole (I; R = Ph) is formed by heating aminoguanidine carbonate with benzoyl chloride. This method was found unsatisfactory and it seemed possible that 1-benzoyl-*S*-methyl*iso*thiosemicarbazide (II; R = Ph) (Part III, *J.*, 1949, 1918) might react with ammonia or primary or secondary amines to give the benzamidoguanidine (III) or the corresponding alkyl derivatives of (III), which, it was expected, would be readily cyclised to 5-amino-3-phenyl-1 : 2 : 4-triazoles.


(I.)


$R{\cdot}CO{\cdot}NH{\cdot}N{:}\underset{SMe}{C}{\cdot}NH_2$
(II.)

$R{\cdot}CO{\cdot}NH{\cdot}N{:}C(NH_2)_2$
(III.)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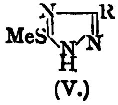
(V.)

When (II; R = Ph) was heated with alcoholic ammonia, *iso*propylamine, or diethylamine, 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (IV; R = Ph) and 5-methylthio-3-phenyl-1 : 2 : 4-triazole (V; R = Ph) were formed in each case. The same reaction was observed when the tertiary bases, pyridine or triethylamine, were used. The *p*-anisoyl compound (II; R = *p*-$MeO{\cdot}C_6H_4$) with ammonia or triethylamine gave the corresponding oxadiazole and triazole, but the amount of the latter product was small. 5-*Methylthio*-3-p-*chlorophenyl*-1 : 2 : 4-*triazole* was obtained by the action of triethylamine on 1-*p*-chlorobenzoyl-*S*-methyl*iso*thiosemicarbazide and also by methylation of the corresponding thiol. These results are in contrast to the behaviour of 1-benzoyl-*S*-methyl*iso*thiosemicarbazides with alcoholic solutions of sodium alkoxides (Part III) which under similar conditions give 5-alkoxy-3-phenyl-1 : 2 : 4-triazoles. However, the crude alkoxy-triazoles, prepared in this way, were found to contain a small amount of sulphur which was difficult to remove by crystallisation and necessitated a method of purification involving dissolution in acids and alkalis. It is probable that small amounts of the methylthio-triazoles were formed in this reaction. Since the parent 1-benzoylthiosemicarbazides give the same product (*i.e.*, 3-phenyl-1 : 2 : 4-triazole-5-thiols) with alcoholic solutions of organic bases or sodium alkoxides (Part II, *J.*, 1949, 1163) it might be supposed that the 5-alkoxytriazoles were formed by the action of sodium alkoxides on 5-methylthio-triazoles. This was disproved by showing that 5-methylthio-3-phenyl-1 : 2 : 4-triazole was recovered unchanged after long refluxing with sodium ethoxide solution. The same methylthio-group has been shown (Part I, *J.*, 1949, 1160) not to be replaced on heating the substance with amines and it has now been observed that 5-methoxy-3-*p*-methoxyphenyl-1 : 2 : 4-triazole is not attacked by hot ammonia.

In the above reactions of 1-benzoyl-*S*-methyl*iso*thiosemicarbazides with amines, separation of the products was readily effected by dissolution of the triazole in sodium hydroxide solution. In each case, the crude triazole when precipitated from the clarified alkaline solution, had approximately the expected sulphur content. However, when piperidine was used as the amine, the triazole fraction had much less than half of the expected amount of sulphur and was eventually separated into 5-methylthio-3-phenyl-1 : 2 : 4-triazole (V; R = Ph) and *5-piperidino-3-phenyl-*1 : 2 : 4-*triazole*, which have very similar solubilities.

Benzamidoguanidines (III; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl) were obtained by warming the corresponding benzhydrazides with *S*-methyl*iso*thiourea sulphate and alkali, and the compound (III; R = Ph) was also obtained by treatment of aminoguanidine with benzoyl chloride in cold pyridine. These compounds are readily cyclised with loss of water on being heated just below their melting points and in this manner very satisfactory yields of 5-amino-3-phenyl-, *5-amino-*3-p-*methoxyphenyl-*, and *5-amino-*3-p-*chlorophenyl-*1 : 2 : 4-*triazole* (I; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl) were obtained. This cyclisation was also carried out with an alcoholic solution of sodium ethoxide (in moderate yield) but could not be effected with sulphuric or phosphoric acid (cf. the cyclisation of 1-benzoylthiosemicarbazides, Part II).

When benzhydrazide was treated with *S*-methyl-*NN*-pentamethylene*iso*thiourea, 5-piperidino-3-phenyl-1 : 2 : 4-triazole was formed directly. The intermediate benzamidoguanidine in this case appears to be cyclised during the isolation. The corresponding *p*-methoxyphenyl *compound* was obtained by using *p*-anishydrazide.

EXPERIMENTAL.

Reaction of 1-*Benzoyl-*S-*methyl*iso*thiosemicarbazide with Ammonia*.—The *S*-methyl*iso*thiosemicarbazide (4·2 g.) and alcohol (25 c.c.) containing dry ammonia gas (1·9 g.) were set aside for 12 hours and then refluxed for 4 hours. The solvent was evaporated under reduced pressure, and the residue triturated with *N*-sodium hydroxide (50 c.c.) and filtered. The insoluble residue, which was sulphur-free (2·3 g.; m. p. 236°), was crystallised from alcohol, giving colourless prisms (1·8 g.) of 2-amino-5-phenyl-1 : 3 : 4-oxadiazole, m. p. 243°, not depressed by an authentic specimen (Fehrenbach and Stollé, *J. pr. Chem.*, 1929, **122**, 289). The original filtrate was made just acid with acetic acid, and the precipitate collected (0·9 g.; m. p. 158—160°) (Found : S, 15·8%) and crystallised from water containing a little alcohol, giving colourless plates (0·6 g.) of 5-methylthio-3-phenyl-1 : 2 : 4-triazole, m. p. 162° (Part I, *loc. cit.*) (Found : C, 56·4; H, 4·3; S, 17·0. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7; S, 16·75%).

With *iso*propylamine (5·0 c.c.) in place of ammonia in the above experiment, the amino-oxadiazole (2·0 g.; m. p. 243°) and the methylthio-triazole (0·5 g.; m. p. 161°) were isolated. With diethylamine, triethylamine, or pyridine very similar results were obtained. The percentages of sulphur in the crude alkali-soluble fractions from these and the preceding experiment were 16·0, 16·7, 16·2, and 16·3 respectively.

Reaction of 1-*Benzoyl-*S-*methyl*iso*thiosemicarbazide with Piperidine*.—When the above experiment was repeated using piperidine (4·0 c.c.) in place of ammonia, the amino-oxadiazole (1·3 g.; m. p. 240°) was isolated as previously (Found : C, 59·6; H, 4·4. Calc. for $C_8H_7ON_3$: C, 59·6; H, 4·3%). The crude alkali-soluble fraction (1·4 g.; m. p. 135—140°) (Found : S, 7·2%) was rubbed in a mortar with N-hydrochloric acid (10 c.c.) for 1 minute and quickly filtered (the whole dissolved on rubbing with twice as much acid for 15 minutes). The residue (0·3 g.; m. p. 152—154°) (Found : S, 15·6%) was crystallised twice from aqueous alcohol giving colourless leaflets (0·2 g.) of the methylthio-triazole, m. p. 162° (Found : C, 56·5; H, 4·6%). The acid extract was precipitated with potassium hydrogen carbonate, the solid collected (1·0 g.; m. p. 170—180°) (Found : S, 0·2%) and crystallised from benzene–light petroleum (b. p. 60—80°) and then twice from benzene giving colourless needles (0·5 g.) of *5-piperidino-3-phenyl-*1 : 2 : 4-*triazole*, m. p. 196° (Found : C, 68·7; H, 6·8; N, 24·6. $C_{13}H_{16}N_4$ requires C, 68·4; H, 7·0; N, 24·6%).

Reaction of 1-p-*Anisoyl-*S-*methyl*iso*thiosemicarbazide with Ammonia*.—The *S*-methyl*iso*thiosemicarbazide (4·8 g.) and alcohol (25 c.c.) containing ammonia (1·8 g.) gave the amino-oxadiazole (Part III, *loc. cit.*), which crystallised from alcohol in large colourless needles (2·8 g.), m. p. 246—247°, and the methylthio-triazole (Part III, *loc. cit.*), which crystallised from aqueous alcohol in colourless leaflets (0·1 g.), m. p. 125° (Found : C, 54·2; H, 4·8. Calc. for $C_{10}H_{11}ON_3S$: C, 54·3; H, 5·0%). A similar result was obtained by using triethylamine (6·3 c.c.) in place of the ammonia, and in both cases the methylthio-triazole was formed in smaller amounts and was more difficult to purify compared with corresponding reactions with 1-benzoyl-*S*-methyl*iso*thiosemicarbazide.

Reaction of 1-p-*Chlorobenzoyl-*S-*methyl*iso*thiosemicarbazide with Triethylamine*.—The *S*-methyl*iso*thiosemicarbazide (4·9 g.), alcohol (30 c.c.), and triethylamine (6·3 c.c.) gave, as above, the amino-oxadiazole (Part III, *loc. cit.*) (2·1 g.) which crystallised from alcohol in colourless needles, m. p. 270°, and *5-methylthio-*3-p-*chlorophenyl-*1 : 2 : 4-*triazole* which crystallised from benzene in hard, refractive, colourless prisms (1·2 g.), m. p. 154° (Found : C, 48·2; H, 3·5; S, 14·2. $C_9H_8N_3SCl$ requires C, 47·9; H, 3·5; S, 14·2%). The same methylthio-triazole was obtained by shaking the triazole-thiol (0·7 g.) with N-sodium hydroxide (5 c.c.), methyl iodide (0·3 c.c.), and alcohol (1 c.c.). The precipitate, crystallised from benzene, gave colourless prisms (0·5 g.), m. p. 153°, not depressed by the compound as prepared above (Found : C, 48·0; H, 3·6%).

*Attempt to cause 5-Methylthio-3-phenyl- or 5-Methoxy-*3-p-*methoxyphenyl-*1 : 2 : 4-*triazole to react with Sodium Ethoxide and Ammonia, respectively*.—The methylthiotriazole (1·9 g.) was refluxed with a solution of sodium (0·8 g.) in alcohol (30 c.c.) for 24 hours and evaporated under reduced pressure. The residue was made just acid with acetic acid, and the solid collected and crystallised from aqueous alcohol, giving colourless leaflets (1·6 g.), m. p. 161—162°, not depressed by admixture with starting material.

The methoxy-triazole (Part III, *loc. cit.*) (0·5 g.) and alcohol (20 c.c.) containing ammonia (1·8 g.) were heated in a sealed tube at 110° for 18 hours. The residue left on evaporation of the solvent crystallised from aqueous alcohol in colourless needles (0·35 g.), m. p. 168—169°, not depressed by admixture with starting material.

Benzamidoguanidine (III; R = Ph).—(*a*) *S*-Methyl*iso*thiourea sulphate (13·9 g.) was added with stirring to ice-cold N-sodium hydroxide (100 c.c.), followed by benzhydrazide (13·5 g.). After storage for 3—4 days at room temperature (smaller yields were obtained after shorter times) the mixture was slowly heated to 50° and kept for 3 hours at this temperature. Purple-tinged crystals separated. The reaction vessel was cooled in a freezing mixture, a rapid stream of carbon dioxide passed in, and, after neutralisation, the solid was collected, washed with water, and dried (12·2 g.; m. p. 180—182°). *Benzamidoguanidine* was soluble in dilute acids but only sparingly soluble in sodium hydroxide solution, and crystallised from water (charcoal) in large colourless refractive prisms, m. p. 184° (decomp.) (Found: C, 54·2; H, 5·5; N, 31·9. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·6; N, 31·5%).

(*b*) Aminoguanidine hydrogen carbonate (6·0 g.) in dry pyridine (50 c.c.) was cooled to 0° and stirred whilst freshly distilled benzoyl chloride (6·0 c.c.) was added during 0·5 hour. After 12 hours' stirring at room temperature, the solvent was removed under reduced pressure, and the residue treated with water (50 c.c.) and made strongly alkaline with 10N-sodium hydroxide. The solid was collected (3·4 g.; m. p. 180—182°) and crystallised from water giving large colourless prisms, m. p. 185° (decomp.) (Found: C, 53·5; H, 5·7%). The alkaline filtrates were examined for amino-triazole but only benzoic acid (1·4 g.; m. p. 121°) was isolated.

The following were obtained in good yield by method (*a*): p-*anisamido*- (III; R = *p*-MeO·C_6H_4), colourless prisms which effloresce on drying (from water), m. p. 218—220° (Found: C, 52·0; H, 5·9. $C_9H_{12}O_2N_4$ requires C, 51·9; H, 5·8%), and p-*chlorobenzamido-guanidine* (III; R = *p*-C_6H_4Cl), colourless prisms (from aqueous alcohol), m. p. 194—196° (Found: C, 45·6; H, 4·3; N, 26·5. $C_8H_9ON_4Cl$ requires C, 45·2; H, 4·2; N, 26·4%). *p*-Chlorobenzhydrazide was much less soluble than the other hydrazides used and the reaction liquid was therefore diluted with an equal volume of alcohol and this solvent subsequently removed under reduced pressure at 50°.

5-*Amino*-3-*phenyl*-1 : 2 : 4-*triazole* (I; R = Ph).—(*a*) Benzamidoguanidine (5·0 g.) was heated in an oil-bath at 220°. Water was eliminated with decrepitation and after 5 minutes the residue was crystallised from water, giving colourless silky needles (3·8 g.), m. p. 186—187°, not depressed by a specimen prepared as described by Benack (*loc. cit.*) (Found: C, 59·8; H, 4·9. Calc. for $C_8H_8N_4$: C, 60·0; H, 5·0%). When benzamidoguanidine (1·8 g.) was added to sulphuric acid (98%; 20 c.c.) at 120° (with stirring), a sublimate of benzoic acid formed. After 0·5 hour's stirring, the mixture was poured on ice; the solid was collected (1·1 g.; m. p. 118°) and by crystallisation from water gave benzoic acid (0·6 g.; m. p. 120°). The acid filtrates contained no diazotisable amine. A similar result was obtained with phosphoric acid-phosphoric oxide.

(*b*) Benzamidoguanidine (1·8 g.) was refluxed with a solution of sodium (1·5 g.) in alcohol (100 c.c.) for 3 hours and the solvent removed under reduced pressure. Water (20 c.c.) was added, the small insoluble residue filtered off, and the filtrate made just acid with acetic acid. The precipitate (0·6 g.; m. p. 184°) was collected and crystallised from water giving colourless needles (0·4 g.), m. p. 186° (Found: C, 60·2; H, 5·2%).

The following were prepared by method (*a*): 5-*amino*-3-p-*methoxyphenyl*- (I; R = *p*-McO·C_6H_4), small colourless plates (from water), m. p. 224—226° (Found: C, 57·1; H, 5·3. $C_9H_{10}ON_4$ requires C, 56·8; H, 5·3%), and 5-*amino*-3-p-*chlorophenyl*-1 : 2 : 4-*triazole* (I; R = *p*-C_6H_4Cl), large colourless needles (from aqueous alcohol), m. p. 227—229° (Found: C, 49·7; H, 3·9. $C_8H_7N_4Cl$ requires C, 49·4; H, 3·6%).

5-*Piperidino*-3-*phenyl*-1 : 2 : 4-*triazole.*—*NN*-Pentamethylenethiourea (6·0 g.) and water (10 c.c.) were shaken together and freshly distilled methyl sulphate (6·0 g.) added. On slight warming of the mixture, a vigorous reaction occurred. The clear solution was refluxed for 0·5 hour and evaporated under reduced pressure. The syrup (which could not be crystallised) was cooled in a freezing mixture, and N-sodium hydroxide added until the product was just alkaline to brilliant-yellow. Benzhydrazide (5·4 g.) was added, and after 3 days the reaction mixture was stirred and heated at 50° for 3 hours. The supernatant liquid was decanted from the sticky precipitate which was hardened by rubbing it with a little 10% acetic acid. The solid was collected (6·7 g.; m. p. 180°) and crystallised from aqueous alcohol, giving colourless needles (5·2 g.), m. p. 196—198°, not depressed by the compound prepared as above (Found: C, 68·5; H, 6·9%).

5-*Piperidino*-3-p-*methoxyphenyl*-1 : 2 : 4-*triazole.*—This *compound*, obtained as was the corresponding phenyl compound, crystallised from aqueous alcohol or benzene-light petroleum (b. p. 60—80°) in colourless platelets, m. p. 206—208° (Found: C, 65·3; H, 6·9. $C_{14}H_{18}ON_4$ requires C, 65·1; H, 7·0%).

Imperial Chemical Industries Limited (Research Laboratories),
Blackley, Manchester, 9.
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117. *Compounds related to Thiosemicarbazide. Part V.*
4 : 5-*Diamino*-3-*phenyl*-4 : 1 : 2-*triazole.*

By Eric Hoggarth.

1 : 4-Dibenzoylthiosemicarbazide reacts with hydrazine to give 3-phenyl-1 : 2 : 4-triazole-5-thiol, benzhydrazide, and a compound $C_8H_9N_5$, whose reactions indicate that it is 4 : 5-*diamino*-3-*phenyl*-4 : 1 : 2-*triazole*.

The work recorded here arose out of the observation mentioned in an earlier report (Part I, *J.*, 1949, 1160) that the hydrazine salt of 1 : 4-dibenzoylthiosemicarbazide (I) was rapidly decomposed in boiling alcohol with evolution of hydrogen sulphide. It was to be expected that hydrazine, in view of its basic nature, would cause a cyclisation of the dibenzoyl compound corresponding to that observed with 1-benzoylthiosemicarbazides (Part II, *J.*, 1949, 1163) and it was confirmed that with a solution of sodium in alcohol the expected cyclisation of (I) to 3-phenyl-1 : 2 : 4-triazole-5-thiol (II) (and benzoic acid) occurred. However the evolution of hydrogen sulphide with use of hydrazine indicated that, at least in part, interaction with elimination of the (potential) thiol grouping was taking place. When 1 : 4-dibenzoylthiosemicarbazide was refluxed with hydrazine and alcohol, a white crystalline sublimate formed. This sublimate was very unstable but a little of it, washed out with water, gave tests for hydrazine and the sulphide ion; it was probably a salt of hydrazine and hydrogen sulphide. In a stream of nitrogen no sublimate formed and absorption in acidified lead acetate solution showed that less than 50% of the theoretical amount of hydrogen sulphide (supposing complete elimination) was actually evolved. The residual solution was shown to contain the triazole-thiol (II), benzhydrazide, and a *compound* $C_8H_9N_5$, the formula of which is obtained by replacement of the thiol group by hydrazine and elimination of the elements of benzoic acid. It was shown that

Ph·CO·NH·NH·CS·NH·CO·Ph

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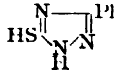

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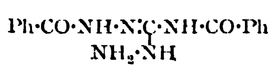
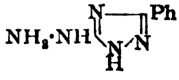


$$\mathrm{Ph{\cdot}CO{\cdot}NH{\cdot}N{:}\underset{NH_2{\cdot}NH}{C}{\cdot}NH{\cdot}CO{\cdot}Ph}$$

(III.)



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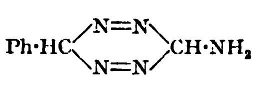

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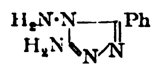

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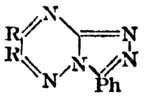
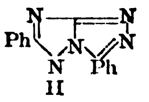


(VII.)



(VIII.)

the triazolethiol was completely inert towards hydrazine under the reaction conditions and it seemed therefore that this new compound arose by a cyclisation of the (hypothetical) dibenzoyldiaminoguanidine (III). Of the three possible structures which must be considered (IV, V, and VI) the first two may be eliminated.

5-Hydrazino-3-phenyl-1 : 2 : 4-triazole (IV) was prepared (but not isolated) by Manchot (*Ber.*, 1910, **43**, 1312) and shown to form a well-defined monobenzylidene and related derivatives. The compound $C_8H_9N_5$ reacted with benzaldehyde or *p*-methoxybenzaldehyde in the presence of a little sodium hydroxide (but not in its absence) to give ***dibenzylidene*** and ***di-p-methoxybenzylidene*** derivatives having melting points quite different from those of the benzylidene derivatives described by Manchot. Further evidence for the 4 : 5-diamino-4 : 1 : 2-triazole structure was found in the ready condensation with α-diketones (benzil, diacetyl) to give 1 : 2 : 4 : 7 : 9-***penta-azaindenes*** (VII; R = Ph or Me). Although these reactions seem conclusive in favour of structure (VI) it is known that dihydro-1 : 2 : 4 : 5-tetrazines are readily isomerised to *N*-aminotriazole derivatives. Thus Curtius, Darapsky, and Müller (*Ber.*, 1907, **40**, 815) found that dihydro-1 : 2 : 4 : 5-tetrazine itself gave 4-amino-4 : 1 : 2-triazole on fusion. It was possible therefore, that the compound $C_8H_9N_5$ had the dihydrotetrazine structure (V) and was giving derivatives of (VI) under the influence of alkaline catalysts. This possibility was disproved by showing that the compound was unchanged by fusion and recovered from the dibenzylidene compounds, mentioned above, by hydrolysis. Dihydrotetrazines in general are very readily oxidised to the corresponding tetrazines, many of which have an intense purple colour. The compound $C_8H_9N_5$ did not develop such a colour with oxidising agents but when first isolated was purple, the intensity varying from experiment to experiment. This colour, which may be ascribed to the oxidation of a trace of dihydrotetrazine contaminant, was lost on crystallisation.

Under mild conditions, 4 : 5-diamino-3-phenyl-4 : 1 : 2-triazole gave a ***monobenzoyl*** compound from which, by acid hydrolysis, the parent diamine could be recovered. By further reaction of the monobenzoyl derivative, or of the diamine with excess of benzoyl chloride, a ***substance*** $C_{22}H_{15}ON_5$ was obtained, corresponding to a dibenzoyl compound less the elements of water. On hydrolysis of this a ***compound*** $C_{15}H_{11}N_5$ was obtained which probably has the triazolotriazole structure (VIII).

EXPERIMENTAL.

Reaction of 1 : *4-Dibenzoylthiosemicarbazide with Sodium Ethoxide Solution.*—The dibenzoyl compound (3·8 g.) was refluxed with a solution of sodium (1·2 g.) in alcohol (50 c.c.) until the copious yellow precipitate (the sodium salt of the dibenzoyl compound) had disappeared (*ca.* 16 hours). After cooling, the precipitated sodium benzoate (1·8 g.) was collected and dissolved in water, and the benzoic acid precipitated with acid (1·2 g.; m. p. 119—120°). The initial filtrate was evaporated under reduced pressure, and the residue dissolved in water (30 c.c.), filtered (charcoal), and precipitated with hydrochloric acid.

The 3-phenyl-1 : 2 : 4-triazole-5-thiol (2·0 g.; m. p. 255—256°) was crystallised from water, giving colourless needles (1·6 g.), m. p. and mixed m. p. 256—257° (Part I, *loc. cit.*) (Found: C, 54·3; H, 4·0. Calc. for $C_8H_7N_3S$: C, 54·2; H, 4·0%).

Reaction of 1 : 4-*Dibenzoylthiosemicarbazide with Hydrazine*.—A mixture of the dibenzoyl compound (6·0 g.), alcohol (50 c.c.), and hydrazine hydrate (8·0 c.c. of 50%) was refluxed in a stream of nitrogen until evolution of hydrogen sulphide ceased (8—9 hours). The effluent gas was washed in acidified lead acetate solution, and the lead sulphide collected in a Gooch crucible and dried at 110° (2·2 g.). The residual solution was evaporated under reduced pressure, the residue dissolved in water (50 c.c.), and hydrochloric acid was added, with good cooling, until the mixture was just acid to Congo-red paper. The precipitate (2·1 g.; m. p. 235—240°) was crystallised twice from water, giving colourless needles (0·7 g.) of 3-phenyl-1 : 2 : 4-triazole-5-thiol, m. p. 256—257° (Found: C, 54·5; H, 4·3%). The acid filtrates were evaporated under reduced pressure, the residue was cooled strongly, and 40% potassium hydroxide solution (10 c.c.) was added. The pink-tinged solid was collected (0·4 g.), washed with a little ice-water, and crystallised from water or alcohol, giving large colourless plates of 4 : 5-*diamino*-3-*phenyl*-4 : 1 : 2-*triazole* (0·25 g.), m. p. 224° (Found: C, 55·1; H, 5·3; N, 39·6. $C_8H_9N_5$ requires C, 54·9; H, 5·1; N, 40·0%). The alkaline filtrates were cooled, made just acid with 10% acetic acid, and evaporated under reduced pressure. The dry residue was extracted with chloroform, and the extracts were dried and evaporated, giving benzhydrazide (2·6 g.) which crystallised from benzene as colourless plates, m. p. and mixed m. p. 113° (Found: C, 61·9; H, 5·9. Calc. for $C_7H_8ON_2$: C, 61·8; H, 5·9%).

The diamine (0·5 g.) was melted in an oil-bath at 230° for 15 minutes, cooled, and crystallised from water, giving colourless plates (0·3 g.), m. p. 224°, not depressed by the original substance.

Attempt to cause 3-*Phenyl*-1 : 2 : 4-*triazole*-5-*thiol to react with Hydrazine*.—The thiol (1·8 g.), hydrazine hydrate (5·0 c.c. of 50%), and alcohol (50 c.c.) were refluxed for 36 hours. No hydrogen sulphide was evolved. The solvents were removed under reduced pressure, and water (25 c.c.) was added, followed by hydrochloric acid until the mixture was acid to Congo-red. The precipitate (1·5 g.; m. p. 258°) crystallised from water as colourless plates (1·0 g.), m. p. 258°, not depressed by the original thiol.

4 : 5-*Bisbenzylideneamino*-3-*phenyl*-1 : 2 : 4-*triazole*.—The diamino-compound (1·0 g.), freshly distilled benzaldehyde (1·0 c.c.), alcohol (20 c.c.), and potassium hydroxide (0·1 g.) were refluxed together for 0·5 hours, filtered quickly, and allowed to crystallise. The pale yellow crystals of *bisbenzylideneamino*-compound (1·0 g.) were collected and recrystallised from alcohol, giving yellow needles (0·6 g.), m. p. 202—203° (Found: C, 75·1; H, 5·0; N, 20·3. $C_{22}H_{17}N_5$ requires C, 75·2; H, 4·8; N, 20·0%). There was no precipitate when the same mixture but without the potassium hydroxide was boiled for 24 hours. This compound (0·3 g.) was boiled for 1 minute with concentrated hydrochloric acid (5 c.c.), and excess of acid evaporated in a dish. N-Hydrochloric acid (5 c.c.) was added, the oily drops of benzaldehyde were removed with ether, and the residual aqueous solution was clarified (charcoal) and treated with 40% potassium hydroxide solution. The pearly leaflets precipitated were collected, washed with ice-water, and crystallised from water, giving colourless plates (0·1 g.), m. p. 225°, not depressed by admixture with the diamine (Found: C, 54·5; H, 5·1%).

By use of *p*-methoxybenzaldehyde in place of benzaldehyde, the corresponding 4 : 5-*bis*-p-*methoxybenzylideneamino-triazole* was obtained as yellow clumps of needles (1·0 g.), m. p. 165° (from alcohol) (Found: C, 69·9; H, 4·6; N, 17·1. $C_{24}H_{21}O_2N_5$ requires C, 70·1; H, 5·1; N, 17·0%). Hydrolysis of this compound with acid gave *p*-methoxybenzaldehyde and the original diamine, m. p. and mixed m. p. 225°.

3 : 5 : 6-*Triphenyl*-1 : 2 : 4 : 7 : 9-*penta-azaindene* (VII; R = Ph).—The diamine (1·0 g.), benzil (1·2 g.), and alcohol (30 c.c.) were refluxed for 12 hours and cooled, whereupon benzil (1·0 g.) (only) separated. The original mixture, but with the addition of sodium hydroxide (0·05 g.), became intensely yellow on heating, and crystals separated. After 1 hour, the mixture was cooled, and the solid collected and crystallised from 2-ethoxyethanol giving the *penta-azaindene* as square, deep-yellow plates (1·0 g.), m. p. 250° (Found: C, 75·5; H, 4·5; N, 20·1. $C_{22}H_{15}N_5$ requires C, 75·6; H, 4·3; N, 20·1%).

3-*Phenyl*-5 : 6-*dimethyl*-1 : 2 : 4 : 7 : 9-*penta-azaindene* (VII; R = Me).—The above experiment was repeated with diacetyl (1·0 c.c.) in place of benzil, giving a yellow *product* which crystallised from aqueous diethylformamide in long deep-yellow needles (0·6 g.), m. p. 203° (Found: C, 64·2; H, 4·8; N, 31·1. $C_{12}H_{11}N_5$ requires C, 64·0; H, 4·9; N, 31·1%).

Action of Benzoyl Chloride on 4 : 5-*Diamino*-3-*phenyl*-4 : 1 : 2-*triazole*.—The diamine (1·8 g.) was dissolved in dry pyridine (75 c.c.) at 80° and a solution of benzoyl chloride (1·5 g.) in dry pyridine (10 c.c.) added with shaking. After 10 minutes, the pyridine was evaporated under reduced pressure, the residue treated with water (100 c.c.), and the solid collected, washed with water, and dried at 100° (3·0 g.; m. p. 258°). From alcohol, in which it is not very soluble, this *benzoyl* derivative crystallised in colourless leaflets, m. p. 264—266° (Found: C, 64·1; H, 4·9; N, 25·2. $C_{15}H_{13}ON_5$ requires C, 64·5; H, 4·7; N, 25·1%). The same compound was obtained by rubbing the diamine (0·5 g.) with benzoyl chloride (0·5 g.), whereupon a vigorous reaction took place. Pyridine (1 c.c.) was added, the mixture cautiously warmed to effect dissolution, and ice and water (20 g.) were added. The solid was collected and crystallised as above, giving colourless leaflets (0·4 g.), m. p. 266°. This compound (0·75 g.) was refluxed with 2-ethoxyethanol (15 c.c.) and concentrated hydrochloric acid (2·5 c.c.) for 0·5 hour and the solvent removed under reduced pressure. The residue was treated with N-sodium hydroxide (5 c.c.), and the solid collected and crystallised from water, giving colourless plates (0·25 g.), m. p. 224°, not depressed on admixture with the diamine. The benzoyl compound was stable to boiling N-sodium hydroxide, giving, on cooling, a crystalline sodium salt from which the original benzoyl compound was recovered by dissolution in N-hydrochloric acid and neutralisation with potassium hydrogen carbonate.

The above benzoyl compound (0·5 g.), benzoyl chloride (1 c.c.), and dry pyridine (10 c.c.) were refluxed for 12 hours. Water (15 c.c.) was added (too much water precipitated a tar), and the solid collected and washed, until nearly colourless, with alcohol. From alcohol the *substance* crystallised in colourless needles (0·4 g.), m. p. 196° (Found: C, 72·2; H, 4·0. $C_{22}H_{15}ON_5$ requires C, 72·3; H, 4·1%). The same substance was obtained from the original diamine (0·5 g.), benzoyl chloride (1·0 c.c.), and pyridine (10 c.c.), and crystallised from alcohol in colourless needles (0·45 g.), m. p. 196—198° (Found:

C, 72·4; H, 4·2%). This substance (2·8 g.), concentrated hydrochloric acid (5·0 c.c.), and 2-ethoxyethanol (50 c.c.) were refluxed for 3 hours. The solvent was removed under reduced pressure, and the residue dissolved in water (100 c.c.) and neutralised with potassium hydrogen carbonate. The solid was collected (2·0 g.; m. p. 230—235°) and crystallised from alcohol, giving (?) 5 : *5′-diphenyl-*2 : 3-*dihydro-*4′ : 1′ : 2′-*triazolo*(4′ : 3′-2 : 3)-1 : 2 : 4-*triazole* (VIII) as colourless felted needles (1·5 g.), m. p. 257° (Found: C, 68·6; H, 4·5; N, 27·1. $C_{15}H_{11}N_5$ requires C, 69·0; H, 4·2; N, 26·8%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED (RESEARCH LABORATORIES),
BLACKLEY, MANCHESTER, 9.

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118. *Covalency, Co-ordination, and Chelation. Part III.*

By W. J. LILE and R. C. MENZIES.

The changes in covalency on passing from quadrivalent platinum through tervalent gold to bivalent mercury are discussed with reference to the derived organometallic pseudo-atoms and ions and the additive compounds of some of the latter with amines. The further changes on proceeding to tervalent thallium, quadrivalent lead, and bismuth are outlined.

Similar changes passing down sub-groups IIIB, IVB, and VB to the same metals are also discussed. A few illustrative experiments are described.

THE co-ordination numbers (C.N.) characteristic of the elements from Os (76) to Po (84) in their highest valency states are now well established in inorganic compounds, and pass from a maximum of 8 at osmium (as in OsF_8) through 6 (IrF_6, $[PtCl_6]''$) to a minimum of 4 in gold, *e.g.*, $(Au\ en_2)Br_3$, and in mercury, *e.g.*, $[HgI_4]''$. Beyond this point the maximum C.N. remains at 6 for the next three elements, as shown by the thalli-, plumbi-, and bismuthi-chloride ions, rising finally to 8 again in the acetylacetone derivative of polonium (Servigne, *Compt. rend.*, 1933, **196**, 264).

In lower-valency states a minimum of 2 is found in the same place, as illustrated by $[Au,2CS(NH_2)_2]Cl$, and by the fact that mercurous chloride does not add pyridine, but is decomposed by it, giving mercury and the pyridine complex of mercuric chloride (Lang, *Ber.*, 1888, **21**, 1578).

Definite organo-metallic compounds of osmium and iridium have not yet been described, although Lichtenwalter (Thesis, Iowa State College, 1939, pp. 59, 60) obtained small amounts of amorphous material containing carbon and metal when the trichlorides were treated with phenylmagnesium bromide.

In all its compounds, inorganic, organic and complex, quadrivalent platinum has a co-ordination number of 6, the bonds being directed to the corners of an octahedron (Werner, *Vierteljahrschrift Naturf. Ges., Zurich*, 1917, **62**, 553). Where one atom of quadrivalent platinum appears to be surrounded by less than six other atoms or groups, as in the trimethylplatinum halides (Part I, *J.*, 1933, 1292), association always occurs. Again trimethylplatinum acetylacetone, the single formula for which suggests a co-ordination number of 5 for the metal, was shown (*J.*, 1928, 565) to be bimolecular in benzene, as were later the ethyl acetoacetate and dipropionylmethane derivatives (*J.*, 1933, 21). Another example of the same behaviour has now been provided by the new monopyridine derivative of trimethylplatinic iodide (Gibson, Ewens, and Foss, *Nature*, 1948, **162**, 693), which is also bimolecular in benzene.

The 6-co-valency of quadrivalent platinum, in three dimensions, and the stability of its methyl compounds and of its co-ordination compounds with β-diketones, with ammonia, and with organic amines, are all well established, both organic and organometallic compounds being built on the same plan.

The work of Gibson and his school on the organic derivatives of gold, summarised in his Presidential Address to the British Association (Cambridge, 1938), has established that tervalent gold is 4-co-ordinate in its inorganic, organic, and complex compounds, the metal lying at the centre of a square and the other atoms or groups at the four corners. Brain and Gibson, in particular (*J.*, 1939, 765), attempted, but failed, to prepare a stable compound containing 5-co-ordinate auric gold. All that has been said about quadrivalent platinum and the octahedron may, with equal truth, be said about tervalent gold and the square. Moreover, within the framework of the above, both gold and platinum in both their inorganic and organometallic compounds form well-defined and stable compounds with β-diketones and with amines, the stability of their derivatives with ethylenediamine having been again demonstrated by Gilman and Wood's preparation (*J. Amer. Chem. Soc.*, 1948, **70**, 550) of bistrimethylgold–ethylenediamine, decomposing at 94—98°, while their trimethylgold from which it is derived decomposes below −40°.

The organometallic compounds of mercury (*e.g.*, diphenylmercury, alkylmercury halides) do not form stable compounds with either β-diketones or amines, although they are soluble in pyridine and ethylenediamine, from which they are recovered unchanged. Evidence of combination is, however, provided by Maynard and Howard's observation (*J.*, **1923**, **123**, 963) that the conductivity of an aqueous solution of methylmercury acetate was increased by the addition of pyridine. This suggests co-ordinate combination of the pyridine and the methylmercury group and extrusion of the acid radical as an ion, leaving the C.N. of mercury unchanged. There is yet no evidence that mercury in its organometallic derivatives ever has a higher covalency than 2.

Both valency and co-ordination number of organometallic compounds thus decrease on approaching mercury, and on passing beyond it a new and different structure appears, of which the strongly alkaline nature of the thallous and dialkylthallium hydroxides is an early indication, as is the reactivity of the third alkyl group in the trialkylthallium compounds. These changes resemble those found on passing towards and beyond an inert gas (cf. Berry and Lowry, *J.*, 1928, 1765; Hartmann, *Z. Naturforsch.*, 1947, **2**, *a*, 489). The mercury atom and the thallous ion are related as are argon and potassium, and the mercury dialkyls to the dialkylthallium ions as methane to the ammonium ion.

The alkylmercury halides and the dialkylthallium ions differ from the trialkyl derivatives of platinum and from the dialkyl derivatives of gold, but resemble each other, in not forming stable compounds with pyridine or with ethylenediamine; both, however, are soluble in these solvents. In the compounds of platinum and gold, the forces attaching these addenda to the molecule are of a higher order than those between solvent and solute. In the compounds of mercury, thallium, and lead, they are of the same order, organometallic lead complexes with pyridine and ammonia being unstable; thus diphenyl-lead dibromide forms a compound with four molecules of pyridine which is described as being stable in a pyridine atmosphere, and also with two molecules of ammonia, which can be removed by the passage of air (Pfeiffer, Truskier, and Disselkamp, *Ber.*, 1916, **49**, 2448). This is a contrast to the behaviour of the dipyridyl derivative of trimethylplatinum iodide, which, as described in Part II (Lile and Menzies, *J.*, 1949, 1168), is unattacked by boiling with dilute acetic or hydrochloric acid, 2N-ammonia, or sodium hydroxide. This decrease of the power of attachment is general. Tetramethylplatinum, for instance, is unaffected by iodine, but the tetra-alkyl derivatives of lead are readily decomposed by it. The trialkylbismuths are spontaneously inflammable in air.

Tetramethylplatinum, again, has no melting point, and is tetrameric in the solid state. Diphenylmercury, trimethylthallium, tetraethyl-lead, and triphenylbismuth are all unimolecular (Ghira, *Gazzetta*, 1894, **24**, 312; Abbott, Doctoral Thesis, Iowa State College, 1942, p. 28; Menzies and Overton, *J.*, 1933, 1292; Challenger and Goddard, *J.*, 1920, **117**, 771; see also p. 620).

Although Challenger and Parker (*J.*, 1931, 1462) and Challenger and Richards (*J.*, 1934, 409) have prepared pyridine derivatives of phenylthallium dihalides, and Molnikoff and Gratschewa (*J. Russ. Phys. Chem. Soc.*, 1935, **67**, 1768) those of ethylthallium dibromide, it is shown below that not only methylmercury iodide, but also dimethyl- and diethyl-thallium halides are recovered unchanged on adding water to their solutions in pyridine or ethylenediamine. It is also shown that diphenylmercury, triphenyl-antimony and -bismuth, and tetraphenyl-lead separate unchanged from their solutions in organic solvents containing also ethylenediamine, *i.e.*, under conditions which convert the trimethylplatinum and dialkylgold compounds into stable complexes. If thallium resembles mercury and differs from platinum and gold in not forming stable compounds with organic amines in its dialkyl and diaryl derivatives, it resembles them in forming the stable dialkylthallium derivatives of β-diketones (Menzies, Sidgwick, Cutcliffe, and Fox, *J.*, 1928, 1288). Here, as often, carrying a charge helps both initial attachment and subsequent co-ordination, the familar arrow being electrically supported near the target. These stable, volatile compounds display both the stable combination leading to definite and reproducible composition, and the less stable form involving forces of the same order as those involved in solution. Their association in benzene depends on the concentration (*J.*, 1932, 2734). The corresponding platinum compounds display double molecular weights in benzene at all concentrations.

The elements and groups attached to the heavy metals preceding mercury are more firmly held and in more definite positions than those following it, around which also the form taken by co-ordination is frequently different. 4-Covalent quadrivalent lead, for example is tetrahedral, but optically active lead compounds have not yet been described, racemisation after their attempted preparation possibly taking place on the lines suggested by Garner (*Proc.*,

1912, 28, 67). This loosening becomes apparent on approaching thallium, lead, and bismuth, both from above and from the left. Practical applications of this have been made by Challenger and Ridgeway and by Goddard and Goddard (*J.*, 1922, 121, 104, 256) who used triphenylbismuth as a phenylating agent for the earlier members of Group V, and for mercuric and thallic chlorides.

EXPERIMENTAL.

Action of Ethylenediamine and Pyridine on Methylmercury Iodide.—The ethylenediamine used for this and for the dialkylthallium halides was part of a consignment of 38½ lb. purchased from the Beresworth Laboratories of Framlingham, Mass., early in 1937 and kept since in stoppered bottles; in 1949 it had become light brown and had taken up a little water. It was kept for a few days over potassium hydroxide and then distilled twice from sodium wire. It then boiled at 116—117°/740 mm. and titration by N-sulphuric acid, with methyl-red as indicator, showed a purity of 98·7%. The pyridine used was distilled from a good commercial sample, the fraction of b. p. 114°/745 mm. being used. The methylmercury iodide was the same sample as that used in Part I; it melted at 142—145°, and after drying (P_2O_5), at 145—146°. A sample was dissolved in cold pyridine and reprecipitated by addition of water; after separation and drying (P_2O_5) it melted at 143—144°. A sample was then dissolved in the above purified ethylenediamine, the solution boiled, and water added; a little solid separated out, m. p., after drying over sulphuric acid, 142°. On adding hydrochloric acid to the filtrate, much more solid was again precipitated; m. p. (P_2O_5) 145°, mixed m. p. with original methylmercury iodide 145—146°.

Precipitation on adding water is apparently much more complete with solutions of methylmercury iodide in pyridine than with those in ethylenediamine.

Action of Ethylenediamine on Dialkyl- and Diaryl-thallium Halides.—In most cases mixed m. p.s of the substances before and after recovery afford sufficient evidence of identity, but since the dimethyl- and diethyl-thallium halides have no m. p.s, another means of identification is supplied by the unique and unexplained patterns formed by these substances on the surfaces of drops of their hot solutions cooled on a microscope slide (see *Nature*, 1931, **128**, 907). All these halides are very soluble in anhydrous ethylenediamine, but in contrast to the behaviour of trimethylplatinic iodide they are reprecipitated by water, and even if the halides are boiled with the amine, on subsequent addition of water, the above patterns can be obtained just as if the amine had not been used, formation being occasionally facilitated in both cases by addition of a little of the corresponding alkali halide.

Diphenylthallium bromide does not form these patterns, but analysis of a sample dissolved in anhydrous ethylenediamine and then left until dry over sulphuric acid indicated that, apart from a little adhering ethylenediamine, it was recovered unchanged (Found: C, 33·9; H, 2·4; Br, 16·7; N, 0·68. Calc. for $C_{12}H_{10}TlBr$: C, 32·8; H, 2·3; Br, 18·24; N, 0%. Calc. for $C_{12}H_{10}TlBr,NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$: N, 5·6%). The high carbon and low bromine figures are probably due to the presence of diphenylthallium chloride.

Pyridine has so long been used for recrystallisation of dialkyl- and diaryl-thallium halides that further evidence of their separating unchanged is unnecessary.

Action of Ethylenediamine on Triphenylantimony, Triphenylbismuth, Diphenylmercury, and Tetraphenyl-lead.—Triphenylantimony (m. p. 51°) was prepared by the action of phenylmagnesium bromide on freshly distilled antimony trichloride, b. p. 216—217° (Pfeiffer and Heller, *Ber.*, 1904, **37**, 4621). The antimony was determined by heating with nitric and sulphuric acids, reduction by sulphur dioxide, boiling off excess of the latter, and iodometric titration (Found: Sb, 34·7, 34·5. Calc. for $C_{18}H_{15}Sb$: Sb, 34·5%). Triphenylbismuth (m. p. 78·5°) was similarly prepared from phenylmagnesium bromide and bismuth trichloride (Pfeiffer and Pletsch, *ibid.*, p. 4622). Tetraphenyl- and triphenyl-lead were prepared together by the action of phenylmagnesium bromide on lead chloride and separated by acetone, in which the latter is easily soluble, followed by recrystallisation from chloroform [Found, for triphenyl-lead: Pb, 47·5 (as sulphate). Calc. for $C_{18}H_{15}Pb$: Pb, 47·2%. Found, for tetraphenyl-lead: Pb, 39·1. Calc. for $C_{24}H_{20}Pb$: Pb, 40·2%].

Triphenylantimony, insoluble in hot aqueous ethylenediamine, dissolves readily in the anhydrous solvent. This solution, after addition of alcohol, was evaporated until solid separated; after recrystallisation from alcohol, this melted at 49—50° (mixed m. p. with triphenylantimony, 49—51°).

Action of Ethylenediamine on Other Phenyl-Metal Derivatives.—The compounds were dissolved in benzene, ethylenediamine added, and the solution evaporated to give a solid, as follows:

Compound.	Original.	M. p.	Product.	M. p.	Mixed m. p.
$Pb(C_6H_5)_4$	White needles	224°	White crystals	219°	221°
$Bi(C_6H_5)_3$	White needles	77—78	White needles	76	77—78
$Hg(C_6H_5)_2$	White needles	122—124	Rhombic plates	122—123	122—123

Ethylenediamine therefore does not appear to attack phenyl-metal derivatives in the absence of an acid group.

Triphenylantimony dibromide was made (13 g., 90% yield) by mixing solutions of triphenylantimony (10 g.) and a slight excess of bromine in light petroleum, filtration, and recrystallisation from the same solvent (charcoal); m. p. 214—215° (Michaelis and Reese, *Annalen*, 1886, 233, 48, gave m. p. 216°) (Found: Sb, 24·3. Calc. for $C_{18}H_{15}SbBr_2$: Sb, 23·8%). The high m. p. and consequent stability are in contrast with the properties of triphenylbismuth dibromide, which decomposes in boiling benzene.

Triphenylantimony dichloride was prepared similarly as long colourless needles (up to 8 cm. long); m. p. 143° (Found: Sb, 30·2, 29·9, 29·9. Calc. for $C_{18}H_{15}SbCl_2$: Sb, 28·8%).

Triphenylantimony sulphide was prepared (theoretical yield) by passing hydrogen sulphide into a

cooled alcoholic solution of triphenylantimony dibromide saturated with ammonia; m. p. 112° (Kaufmann, *loc. cit.*, p. 2765, gives m. p. 119—120°) (Found: Sb, 31·4. Calc. for $C_{18}H_{15}SbS$: Sb, 31·6%). The compound is apparently more soluble in alcohol than stated by Kaufmann, 3·7 g. dissolving readily in 30 c.c. of boiling alcohol. It crystallises in needles on cooling. The alcoholic mother-liquors, on cooling, deposit large, colourless, rhombic plates, m. p. 51°, evidently of triphenylantimony re-formed by decomposition of the sulphide. Similarly, a benzene–hexane solution deposits crystal of rhombic sulphur on standing for some days.

The similar treatment (Michaelis and Polis, *Ber.*, 1887, **20**, 57) of triphenylbismuth dichloride or dibromide leads to formation of triphenyl bismuth, ammonium halide, and sulphur.

The molecular weights of three of the above compounds were determined cryoscopically in benzene, with the following results:

Compound.	Weight (g.).	Weight of benzene (g.).	Δ.	*M*, found.	*M*, calc.
$Sb(C_6H_5)_3$	0·7179	17·28	0·619°	348·4	352·9
	0·9894	16·16	0·893	351·1	
	1·7445	16·16	1·583	349·2	
$Sb(C_6H_5)_3Br_2$	0·9707	18·24	0·508	536·4	512·7
	1·4344	18·24	0·758	531·1	
	1·9257	18·24	1·019	530·8	
$Sb(C_6H_5)_3S$	0·2647	15·08	0·196	458·5	385
	0·4797	15·08	0·380	428·7 *	

* During this determination, some decomposition occurred, and the solution became milky.

Triphenylbismuth and its Dichloride.—By passing chlorine through a light petroleum solution of triphenylbismuth, the corresponding dichloride was obtained; m. p. 141° (Michaelis and Polis, *ibid.*, p. 56). Molecular weights were determined cryoscopically in benzene (the constant used was 51·15):

Compound.	Weight (g.).	Weight of benzene (g.).	Δ.	*M*, found.	*M*, calc.
$Bi(C_6H_5)_3$	0·5412	17·49	0·348°	455·3	440·1
	0·9334	17·49	0·602	453·9	
	1·6251	17·49	1·042	456·4	
$Bi(C_6H_5)_3Cl_2$	0·3756	16·63	0·238	485·9	511
	0·5956	16·63	0·379	484·0	
	0·7701	16·63	0·486	488·0	

Challenger and Goddard (*J.*, 1920, **117**, 771) found 427 for the molecular weight of triphenylbismuth in benzene, but as their observed depression was only 0·153°, they were obviously using a more dilute solution. Their figure 498·5 for the molecular weight of the dichloride was calculated from an observed depression of 0·47° and agrees well enough with our value.

Action of Ethylenediamine on Triphenylantimony Dichloride.—The dichloride (4 g.) was dissolved in ether, and ethylenediamine (0·6 c.c., 1 equiv.) added. A white precipitate was produced. This was filtered off, washed with alcohol, and dried, forming minute white crystals, m. p. 206° (decomp. at 235°). The compound was analysed without further purification. The figures show the presence of nitrogen but do not indicate any definite compound (Found: Sb, 23·7; C, 44·4; H, 5·3; N, 6·6. Calc. for $C_{18}H_{15}SbCl_2,NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$: Sb, 24·2; C, 49·6; H, 4·8; N, 5·8%).

Triphenylantimony dichloride was stirred with aqueous ethylenediamine. The solid became curdy. It was filtered off and dried in a vacuum desiccator, but did not contain Cl or N; m. p. 208°; mixed m. p. with the corresponding compound from the dibromide, 210°. It is therefore presumably triphenylantimony dihydroxide.

Action of Ethylenediamine on Triphenylantimony Dibromide.—This dibromide is only slightly soluble in anhydrous ethylenediamine. Addition of ethylenediamine to a solution of the dibromide in alcohol–ether or in benzene gives a white precipitate. This white solid is very deliquescent, and extremely soluble in water, from which it cannot be crystallised; it does not melt below 280°. Heated in a test-tube, it leaves only a slight residue of carbon. It contains bromine and nitrogen, but less than 2% of antimony. With copper sulphate solution it gives the deep blue colour characteristic of ethylenediamine–copper complexes. It would seem, therefore, to be ethylenediaminium dibromide.

Triphenylantimony dibromide (4 g.) was suspended in water, and a few c.c. of ethylenediamine were added. The solid changed in appearance, forming hard cakes. These were broken up, filtered off, washed, and dried, giving a white solid, m. p. 210°, which did not contain either nitrogen or bromine [Found: Sb, 31·8, 33·3. Calc. for $C_{18}H_{15}Sb(OH)_2$: Sb, 31·5%. Calc. for $C_{18}H_{15}SbO$: Sb, 33·1%]; the dihydroxide has m. p. 212°.

Tetraphenyl-lead was heated under reflux with glacial acetic acid, and the diacetate formed was crystallised from dilute acetic acid; it was then dissolved in dilute acetic acid, and hydrogen sulphide passed through the cooled solution. The grey curdy precipitate was separated, extracted with benzene, and the solution crystallised, forming pale yellow prisms, m. p. 130° (decomp. above 90°) [Found: Pb (as sulphate), 51·05; S, 7·94. Calc. for $C_{12}H_{10}PbS$: Pb, 52·69; S, 8·16%]. The sulphur was determined as barium sulphate after fusion with potassium hydroxide and nitrate.

Molecular weights, determined cryoscopically in benzene, were as follows :

Compound.	Weight (g.).	Weight of benzene (g.).	Δ.	*M*, found.	*M*, calc.
$Pb(C_6H_5)_2$	0·2260	15·30	0·097°	780	438
	0·4757	15·30	0·201	792	
$Pb(C_6H_5)_2S$	0·5540	23·08	0·120	1006	393
	0·5540	15·90	0·172	1019	

Acknowledgment is made to the Authorities of the Iowa State College for their courtesy in sending microfilms.

UNIVERSITIES OF BRISTOL AND EDINBURGH.
MID-ESSEX TECHNICAL COLLEGE, CHELMSFORD.

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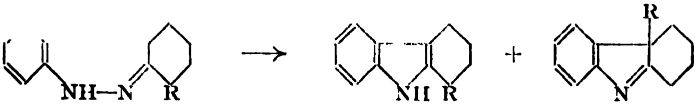
119. *The Fischer Indole Synthesis. Part III. The Cyclisation of the Phenylhydrazones of Some 2-Substituted* cyclo*Hexanones.*

By K. H. PAUSACKER.

Cyclisation of the phenylhydrazones of a number of 2-substituted *cyclo*hexanones has been effected using both dilute sulphuric acid and glacial acetic acid. Whereas sulphuric acid favoured the formation of the neutral tetrahydrocarbazole, the basic tetrahydrocarbazolenine was the principal product formed when glacial acetic acid was used. A detailed investigation of the action of a large number of cyclising agents on the phenylhydrazone of 2-methyl*cyclo*hexanone has also been made. Certain of the tetrahydrocarbazoles obtained have been dehydrogenated by using palladised charcoal.

IT is well known that the phenylhydrazones of 2-substituted *cyclo*hexanones (I) may be cyclised to form both a neutral tetrahydrocarbazole (II) and a basic tetrahydrocarbazolenine (III).



(I.) (II.) (III.)

Pausacker and Schubert (*J.*, 1949, 1384) found that when R = Me the ratio $\frac{\text{yield of (II)}}{\text{yield of (III)}}$ (hereafter termed *a*) was 2·1 when dilute sulphuric acid was used, whereas Lions (*J. Proc. Roy. Soc. N.S.W.*, 1938, **71**, 206) found that, when R = Et, *a* was 0·13 with glacial acetic acid as the cyclising agent. As this comparison is made on two different substances, it was decided to study the influence of these two cyclising agents on compounds of type (I). The results are summarised in Table I.

TABLE I.

	Dilute sulphuric acid.			Glacial acetic acid.		
R.	Yield of (II), %.	Yield of (III), %.	*a*.	Yield of (II), %.	Yield of (III), %.	*a*.
Methyl	45	21	2·1	6 *	61	0·10
Ethyl	44	28	1·6	13	76	0·17
iso*Propyl*	44	18	2·4	16	70	0·23
cyclo*Hexyl*	29	17	1·7	9	79	0·12
Phenyl	54	19	2·8	27	69	0·39

* Appreciable amounts of *N*-acetylphenylhydrazine were also isolated.

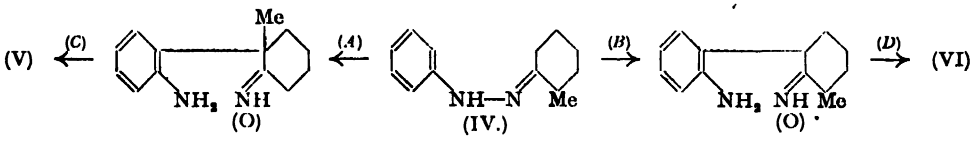
It is thus seen that in every case dilute sulphuric acid gives mainly the tetrahydrocarbazole and glacial acetic acid mainly the tetrahydrocarbazolenine, thus substantiating the results already quoted. An *a priori* hypothesis would predict, by qualitative reasoning, that the stronger acid (sulphuric) should produce a greater proportion of base, whereas the reverse has been found to be the case. This marked difference could be ascribed to different mechanisms operating in these two reactions, although a number of other factors must be considered before any definite conclusion is reached.

One noteworthy difference is that with glacial acetic acid only one phase is present and in dilute sulphuric acid two phases are involved. This may be paralleled with the fact that the Cannizzaro reaction (cf. Alexander, *J. Amer. Chem. Soc.*, 1947, **69**, 289) probably proceeds *via* a different mechanism dependent on whether or not the reaction is homogeneous. When the phenylhydrazone of 2-methyl*cyclo*hexanone (IV) was cyclised in aqueous acetic acid containing 20, 40, 60, 80, and 89% of water (by volume) respectively, the percentage yield of the major product, 11-methyltetrahydrocarbazolenine (V), was 56, 55, 57, 58, and 40% compared with 61% when glacial acetic acid was used. In the first case the reaction mixture was homogeneous throughout, in the second case it was initially heterogeneous and became homogeneous on heating, and in the last three cases it was heterogeneous throughout. It thus appeared that the reaction was not influenced by the number of phases present.

It was thus possible that the difference in reaction may be ascribed to the acid strength of the cyclising agent. When (IV) was refluxed with aqueous solutions of approximately equal molar strength of acetic, monochloro- dichloro- and trichloro-acetic acid, the yields of (V) were 40, 42, 51, and 53% respectively (*N.B.* all these reaction mixtures were heterogeneous). The *K* values of these acids are $1{\cdot}85 \times 10^{-5}$, $1{\cdot}55 \times 10^{-3}$, $5{\cdot}14 \times 10^{-2}$ and $1{\cdot}2 \times 10^{0}$ (?) and yet it is seen that the relative yields of (V) do not vary markedly and tend to increase with increasing acid strength. In view of the remarkable difference between the action of glacial acetic acid and dilute sulphuric acid, this result is very confusing, particularly when it is realised that trichloroacetic acid approaches sulphuric acid in strength, although it has been found that trichloroacetic acid is weaker than sulphuric acid in strong (>2N.) solutions. Thus it would appear that acid strength is not the deciding factor.

Finally, it was considered that as the apparently heterogeneous reaction in aqueous acetic acid gave the same results as when glacial acetic acid was used, the reaction may actually take place in a single phase, as the hydrazone will be partly soluble in the boiling aqueous acetic acid. On the other hand, it would be virtually insoluble in the aqueous sulphuric acid and so the difference between these two reactions may, after all, be due to the number of phases. Accordingly, the cyclisation of (IV) was investigated using alcoholic solutions of sulphuric acid and anhydrous hydrogen chloride. Under these conditions, the initial reactants were soluble, as were the products, with the exception of salts which precipitated during the reaction when hydrogen chloride was used. In the case of sulphuric acid, it was found that although the yield of (V) was greater and the yield of 1-methyltetrahydrocarbazole (VI) was correspondingly smaller, when alcohol was substituted for water as a diluent, the yield of (V) did not approach that obtained with glacial acetic acid. In the case of hydrogen chloride also, the alcoholic solution gave a larger yield of (V) than did the aqueous solution. It may be noted that hydrochloric acid gave a higher yield of (V) than aqueous sulphuric acid of approximately the same normality. Finally dry gaseous hydrogen chloride and a solution of (IV) in dry boiling benzene gave the most surprising results since the yield of (V) was then even greater than with glacial acetic acid and only a very little (VI) was obtained.

In order to harmonise these apparently conflicting findings, it is supposed, on the basis of the accepted mechanism for this reaction (for a summary, see Pausacker and Schubert, *loc. cit.*), that the reaction may proceed as follows:



Now the cyclising agents which favour the formation of (V) are glacial acetic acid, aqueous solutions of acetic acid and its three chloro-derivatives, and hydrogen chloride in benzene The other reagents, in the order in which they favour the yield of (VI), are aqueous sulphuric acid, aqueous hydrogen chloride, alcoholic sulphuric acid, and alcoholic hydrogen chloride. Mr. A. N. Hambly, of this Department, has kindly pointed out that of the first series of media, acetic acid and benzene are protogenic and aprotic respectively, whereas in the latter series both ethyl alcohol and water used are amphiprotic. This suggests that when we have a medium which permits the manifestation of the basic properties of (IV) (*i.e.*, reaction with a proton), then reaction *A*, followed by reaction *C*, is favoured. On the other hand, a medium which tends to decrease the basic characteristics of (IV), by competitive reaction with protons, favours reaction *B* which possibly proceeds by a different mechanism from reaction *A*. Thus the order observed for the second series of solvents may also be explained as water is more protophilic than alcohol and, in addition, there are some indications (cf. " Introduction to

Electrochemistry," Glasstone, p. 310) that sulphuric acid may be more protophilic than hydrochloric acid.

It would now seem that when aqueous solutions of the various acetic acids are used, the reactions must take place in a medium which favours the basic behaviour of (IV). This fact may be accommodated by assuming that the various acetic acids may be dissolved partly in the water and partly in the (IV) (in contrast to the statement made above) and the reaction leading to the principal formation of (V) actually takes place in the acetic acid–(IV) phase.

Thus the different actions of these cyclising agents may be explained by assuming that (IV) has a different proton affinity in the various media used. Up to now, the different formulations of the mechanism of the Fischer indole synthesis have not taken into account the exact role played by the acid catalyst. It would appear in the reaction studied that two alternative mechanisms are simultaneously possible, dependent on the relative proton availability present in the medium. Thus, in future discussions of this reaction it will be necessary to consider, in greater detail, the part played by the catalyst. A kinetic investigation of this reaction is now proceeding with this aim in view.

EXPERIMENTAL.

M. p.s are not corrected.

Preparation of 2-Substituted cyclo*Hexanones.*—2-Methyl-, 2-ethyl-, and 2-*iso*propyl-*cyclo*hexanone were prepared by alkaline hydrolysis of the corresponding 2-carbethoxy-2-alkyl-*cyclo*hexanones, produced by condensation of the appropriate alkyl iodide with the sodio-derivative of 2-carbethoxy-*cyclo*hexanone.

2-*cyclo*Hexyl*cyclo*hexanone was prepared by chromic acid oxidation of 2-*cyclo*hexyl*cyclo*hexanol (cf. Ungnade, *J. Org. Chem.*, 1948, **13**, 361).

2-Phenyl*cyclo*hexanone was prepared by the action of phenylmagnesium bromide on 2-chloro*cyclo*hexanone (Newman and Farbman, *J. Amer. Chem. Soc.*, 1944, **66**, 1551).

Preparation of the Phenylhydrazones.—Equimolar amounts of phenylhydrazine and *cyclo*hexanone were heated (0·5 hour) on the water-bath, first at atmospheric pressure and then under reduced pressure until all the water was expelled.

Cyclisations of the Hydrazones.—The hydrazones were refluxed (0·5 hour) with aqueous sulphuric acid (1 ml. of concentrated acid and 9 ml. of water per g. of hydrazone) or glacial acetic acid (9 ml. per g. of hydrazone). When sulphuric acid was used, the neutral fraction was isolated by extraction with ether and washing first with dilute sulphuric acid and then with water. The 1-substituted tetrahydrocarbazole was isolated by distillation. The sulphuric acid solution and washings were basified with sodium hydroxide solution, and the 11-substituted tetrahydrocarbazolenine isolated by ether-extraction, followed by distillation. When glacial acetic acid was used, the excess of acid was removed by distillation under reduced pressure and the residue treated with water, extracted with ether, and separated into neutral and basic fractions as described above. For yields see Table I. Tables II and III summarise the physical, chemical, and analytical data.

TABLE II.

1-*Substituted tetrahydrocarbazoles.*

	Base.				Picrate.		
Substituent.	B. p./mm.	Formula.	Found: N, %.	Reqd.: N, %.	M. p.[d]	Found: N, %.	Reqd.: N, %.
Ethyl[a]	184—186°/0·8	—	—	—	142°[1]	13·2	13·1
iso*Propyl*	190°/0·6	$C_{15}H_{19}N$	6·9	6·6	117[2]	13·1	12·7
cyclo*Hexyl*	195°/0·4	$C_{18}H_{23}N$	5·6	5·5	140[3]	12·1	11·6
Phenyl[b]	187°/0·3[c]	$C_{18}H_{17}N$	5·8	5·8	133[1]	11·9	11·7

[a] Lions (*loc. cit.*) gives b. p. 200—205°/16 mm. [b] Appreciable amounts of 2-phenyl*cyclo*hexanone were also obtained when dilute sulphuric acid was used. [c] M. p. 99°; crystallised from light petroleum (b. p. 40—60°). [d] Crystallisation from light petroleum of b. p.: [1] 100—120°, [2] 60—90°, [3] 95—135°.

TABLE III.

11-*Substituted tetrahydrocarbazolenines.*

	Base.					Picrate.			
Substituent.	B.p./mm.	M. p.[b]	Formula.	Found: N, %.	Reqd.: N, %.	M. p.	Solvent.[d]	Found: N, %.	Reqd.: N, %.
Ethyl[a]	142°/1·0	—	$C_{14}H_{17}N$	—	—	152°[c]	A	12·8	13·1
iso*Propyl*	166°/0·5	81°	$C_{15}H_{19}N$	6·3	6·6	178	B	13·1	12·7
cyclo*Hexyl*	164°/0·4	79	$C_{18}H_{23}N$	5·9	5·5	171	A	11·6	11·6
Phenyl	184°/1·0	125	$C_{18}H_{17}N$	5·6	5·8	184	A	11·9	11·7

[a] Lions (*loc. cit.*) gives b. p. 160—161°/16 mm. [b] Crystallised from light petroleum (b. p. 40—60°). [c] Lions (*loc. cit.*) gives m. p. 147°. [d] Solvents: A, ethanol; B, light petroleum (b. p. 100—120°).

Dehydrogenation of the Tetrahydrocarbazoles to form Carbazoles.—The 1-substituted carbazole (1·0 g.) was heated for 4 hours at 280—300° with palladised charcoal (0·25 g.) in a stream of hydrogen. The product was extracted with acetone and crystallised from light petroleum (b. p. 40—60°) after distilling off the acetone. The physical, chemical, and analytical data are summarised in Table IV. Picrates were crystallised from benzene.

TABLE IV.

1-Substituted carbazoles.

	Base.				Picrate.		
Substituent.	M. p.	Formula.	Found : N, %.	Reqd. : N, %.	M. p.	Found : N, %.	Reqd. : N, %.
Ethyl	74°	$C_{14}H_{13}N$	7·1	7·2	158°	13·15	13·2
iso*Propyl*	64	$C_{15}H_{15}N$	7·1	6·7	152	12·8	12·8
Phenyl	133	$C_{18}H_{13}N$	5·7	5·8	151	12·4	11·9

*Cyclisation of the Phenylhydrazone of 2-Methyl*cyclo*hexanone in Various Conditions.*—The hydrazone (30 g.) was refluxed for 0·5 hour with the cyclising agents shown in Table V and then worked up as described above. When extraction indicated a small yield of 1-methyltetrahydrocarbazole (VI), only the 11-methyltetrahydrocarbazolenine (V) was purified by distillation.

TABLE V.

Cyclising agent, nature.	amount.	Water, ml.	% Yields of (V).	(VI).	Cyclising agent, nature.	amount.	Water, ml.	% Yields of (V).	(VI).
AcOH,	270 ml.	—	61	6	$CCl_3·CO_2H$,	77·5 g.	191	53	—
,,	216 ml.	54	56	—	Conc. H_2SO_4,	30 ml.	270	21	45
,,	162 ml.	108	55	—	,,	30 ml.	(EtOH, 270 ml.)	36	33
,,	108 ml.	162	57	—					
,,	54 ml.	216	58	—	Conc. HCl,	108 ml.	192	38	40
,,	27 ml.	214	40	—	HCl, gas,	44 g.	(EtOH, 270 ml.)	44	19
$CH_2Cl·CO_2H$,	45 g.	206	42	—					
$CHCl_2·CO_2H$,	61 g.	201	51	—	C_6H_6 *	270 ml.	—	65	4

* Continuously saturated with dry HCl.

Analyses are by Messrs. N. Lottkowitz and N. Gamble. The author thanks his colleagues for many helpful discussions.

UNIVERSITY OF MELBOURNE. [*Received, September 9th, 1949.*]

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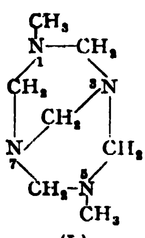
120. *On the Structure of Knudsen's Base and of Related Compounds. Part I.*

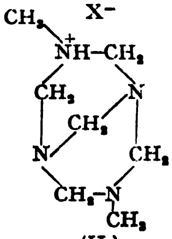
By M. E. FOSS, E. L. HIRST, J. K. N. JONES, H. D. SPRINGALL, A. T. THOMAS, and T. URBAŃSKI.

The corresponding salts of Knudsen's base, and those of the base obtained by treating hexamine dinitrate with hot solvents, are identical with one another and with the corresponding salts of the 1-methylhexamine ammonium cation.

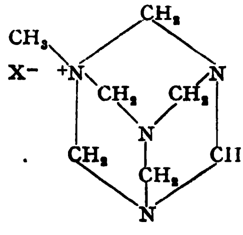
KNUDSEN (*Ber.*, 1914, **47**, 2694) described the preparation of a base, since called "Knudsen's base," in the form of its sulphate, by the action of aqueous formaldehyde on ammonium sulphate. On the basis of carbon, hydrogen, and nitrogen analyses of the salts, Knudsen assigned to the base the structure (I), 1 : 5-dimethylpentamethylenetetramine. The salts were regarded as hydrosalts of type (II).



(I.)



(II.)



(III.)

We had found that, when hexamine dinitrate is treated with hot water, methyl alcohol, ethyl alcohol, *iso*propyl alcohol, or *tert.*-butyl alcohol, the main product isolated, the nitrate, m. p. 195°,* of an organic base (*A*), is independent of the solvent. This compound was identified by carbon, hydrogen, nitrogen, " CH_2 as CH_2O," and nitrate ion analyses, and by mixed m. p., as the hexamine methonitrate (1-methylhexamine 1-nitrate) (III; $X = NO_3$) prepared by Hahn and Walter (*Ber.*, 1921, **54**, 1531) by addition of methyl nitrate to hexamine. This compound was also prepared *via* hexamine methiodide and most carefully investigated in the University of Pennsylvania where it was independently shown that, when hexamine dinitrate is extracted with hot chloroform, hexamine methonitrate is produced (private communication from Professor Marvin Carmack).

We then noticed that corresponding salts of base *A* and of Knudsen's base had many identical chemical and physical properties, indicating that the two bases probably have identical structures. If this is so, then, either the identification of the salts of base *A* as (III), or Knudsen's formulation of the salts of his base as (II), must be in error, and in this connection we note the observation of Hahn and Walter (*loc. cit.*) who had prepared a compound by a reaction similar to Knudsen's reaction (using aqueous formaldehyde, ammonia, and ammonium sulphate) and designated it as (III; $X = NH_4SO_4^-$) on the basis of analyses for carbon, hydrogen, nitrogen, and sulphur only. They did not consider the alternative structure and do not refer to Knudsen's work.

It was therefore decided to re-examine the points named in the headings below.

Evidence for the Identification of the Salts of Base A *as having Structure* (III).—This problem is treated in two parts, showing (*a*) that the main product *A* is the same for a range of solvents, and (*b*) that the product *A* is a nitrate having structure (III; $X = NO_3$).

(*a*) The analytical data and the m. p. and mixed m. p. data for the products *A* isolated by treatment of hexamine dinitrate with several hot solvents are given in Table I and leave little doubt that the various products are identical.

(*b*) The identification of the product *A* as (III; $X = NO_3$) was carried out on the specimen obtained by hot water. The analytical results for the nitrate, picrate, and chloride are given in Table III. For all three, the theoretical figures for carbon, hydrogen, nitrogen, and anion are so similar for the alternative structures (II) and (III) that no differentiation on this basis can be made. The theoretical figures for *N*-methyl and methylene, however, are markedly different, and the experimental data favour the formulation (III) (methylhexamine salts).

TABLE I.

Substance *A* prepared by	C, %.	H, %.	N, %.	CH_2, %.	NO_3^-, %.*	M. p.	Mixed m. p.
H_2O	38·8	6·9	32·2	38·4	28·2	192°	190°
MeOH	38·5	7·0	33·0	38·2	28·0	190	191
EtOH	38·9	6·8	32·4	38·6	28·3	191	190
Pr^iOH	38·8	6·9	32·5	38·0	28·2	192	190
Bu^nOH	38·7	6·9	31·9	38·1	28·3	192	
$CHCl_3$ *	39·0	7·0	32·6	—	27·4	193	

The analytical data reported in this paper were obtained as follows: The C, H, N, and *N*-CH_3 (Herzig–Meyer) determinations were by Drs. Weiler and Strauss (Oxford); CH_2 was determined gravimetrically as CH_2O by dinitrophenylhydrazine, following Brady (*J.*, 1931, 757); NO_3^- and picrate⁻ were determined by nitron, following Cope and Barab (*J. Amer. Chem. Soc.*, 1917, **39**, 509); Cl^- was determined as AgCl.

* Data obtained in the University of Pennsylvania (private communication from Professor Marvin Carmack).

TABLE II.

		M. p. of salt.	
Base.	Nitrate.	Picrate.	Chloride.
(*a*) Authentic methylhexamine	190°	210°	—
(*b*) Base *A* (hot H_2O)	192	212	202°
(*c*) Knudsen's base	190	209 *	202
Mixed *a–b*	190	212	—
Mixed *b–c*	190	209 *	202

* Data obtained by A. T. T. and T. U. at Explosives Research and Development Establishment (E.R.D.E.). The m. p. of this picrate is discussed below.

As was expected, *N*-methyl determinations were not very satisfactory. The Herzig-Meyer micro-procedure might well lead to anomalous results with compounds capable of yielding relatively large amounts of formaldehyde, especially with a tetra-alkylammonium cation such as in (III).

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* The melting of this substance, and of all other new substances discussed in this work, is accompanied by decomposition.

TABLE III.

Analysis of salts of base A *and Knudsen's base.*

	C, %.	H, %.	N, %.	*N*-CH_3, %.	CH_2, %.	Anion, %.	
Found for base *A*	38·8	6·9	32·2	10·0	38·4	28·2	nitrate
Found for Knudsen's base	38·7	7·4	32·2	9·8	38·5	28·3	
Calc. for $C_7H_{15}O_3N_5$ (III; X = NO_3)	38·7	6·9	32·3	13·4	38·8	28·6	
Calc. for $C_7H_{17}O_3N_5$ (II; X = NO_3)	38·4	7·8	32·0	26·5	32·0	28·3	
Found for base *A*	40·6	4·7	25·4	5·0	21·8	59·7	picrate
Found for Knudsen's base	40·6	4·6	25·6	5·2	21·5	59·3	
Calc. for $C_{13}H_{17}O_7N_7$ (III; X = picrate)	40·8	4·4	25·6	7·6	22·0	59·6	
Calc. for $C_{13}H_{19}O_7N_7$ (II; X = picrate)	40·6	5·0	25·5	15·1	18·2	59·3	
Found for base *A*	43·5	8·9	29·8	12·6	43·8	18·7	chloride
Found for Knudsen's base	43·7	9·0	29·5	11·9	44·0	18·7	
Calc. for $C_7H_{15}N_4Cl$ (III; X = Cl)	44·1	7·9	19·4	15·2	44·1	18·6	
Calc. for $C_7H_{17}N_4Cl$ (II; X = Cl)	43·6	8·8	29·1	30·1	36·4	18·4	

Authentic specimens of hexamine methonitrate and methopicrate (III; X = NO_3 or picrate) were prepared from hexamine by the successive action of methyl iodide and silver nitrate or picric acid. Mixed m. p.s of each of these substances and of the corresponding salts of base *A* are given in Table II.

The identity of authentic hexamine methonitrate and the nitrate of base *A* obtained by chloroform has been established by Dr. A. T. Blomquist of Cornell University by microscopic examination (private communication from Professor Marvin Carmack).

As a final check, specimens of authentic hexamine methopicrate and the picrate of base *A* (obtained by hot water) were submitted to Professor F. J. Llewellyn (then of Birmingham University) for comparison by the *X*-ray powder method. He reported that the specimens gave identical patterns (Fig. 1).

The identity of the salts of base *A* with the corresponding salts of the methylhexamine cation is thus established.

Comparison of the Properties of Corresponding Salts of Base A *and of Knudsen's Base.*—Hot water was used to produce the base *A*. The nitrates, picrates, and chlorides of base *A* and of Knudsen's base were prepared and analysed (see Tables II and III). The oily hydroxides prepared from the two bases had identical refractive indices (1·4475 at 20°).

It was found that aqueous solutions of the nitrate, chloride, dichromate, neutral sulphate, and hydroxide of base *A*, on treatment with aqueous picric acid, all gave the same picrate, m. p. 208—209° (m. p.s determined at E.R.D.E.), seemingly identical with the picrate obtained from Knudsen's base.

The findings presented in this section seem to indicate strongly the probable identity of the two bases.

Evidence for the Formulation of the Salts of Knudsen's Base.—The two lines of work described above indicate that salts of Knudsen's base have structure (III), whereas Knudsen (*loc. cit.*) had advocated structure (II). Its picrate was therefore subjected to tests analogous to those used for the identification of the picrate of base *A*.

The first batches of the picrate of Knudsen's base prepared in Manchester (M. E. F., E. L. H., J. K. N. J., H. D. S.) had the m. p. 210° reported from E.R.D.E. All subsequent preparations gave the m. p. 195° recorded by Knudsen. The two specimens of hexamine methopicrate first prepared gave the expected m. p. 210—212°, but a mixed m. p. between them and Knudsen's picrate, m. p. 195°, gave no depression below 195° and all subsequent preparations of hexamine methopicrate in Manchester have shown m. p. 195—198°. It seems probable that hexamine methopicrate is dimorphic and that, the lower-melting dimorph being now obtained, we shall not be able to make again the other modification.

X-Ray powder photographs of Knudsen's picrate and of authentic hexamine methopicrate, kindly supplied by Professor F. J. Llewellyn, showed complete identity (Fig. 2), thus confirming the analytical data—the CH_2 content figure being especially significant—and the rather slight m. p. data.

Further evidence for the methylhexamine cation structure for Knudsen's compounds is furnished by our observation that the direct synthesis of the parent hydroxide of these compounds can be achieved from formaldehyde, methylamine, and ammonia, and that the yield

Fig. 1.

X-Ray powder diagrams for hexamine methopicrate (north and south quadrants) and the picrate of base A (east and west quadrants).

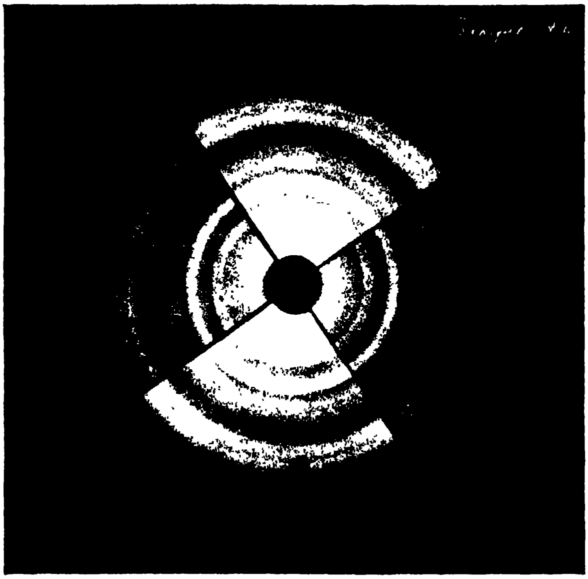
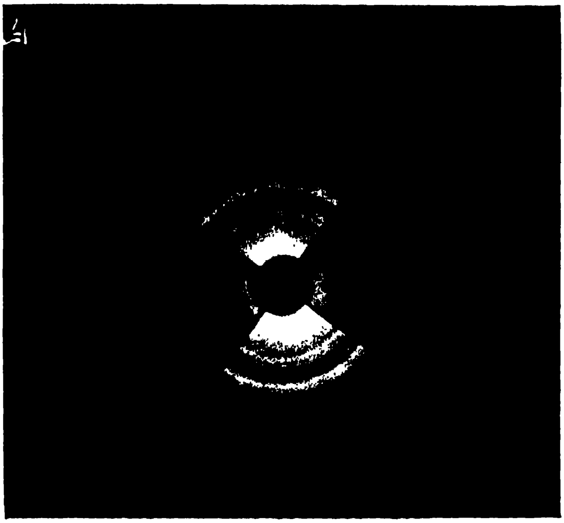


Fig. 2.

X-Ray powder diagrams for hexamine methopicrate (north and south quadrants) and the picrate of Knudsen's base (east and west quadrants).



[*To face p.* 628.

is much better (70%) when the reagents are mixed in the correct stoicheiometric proportions for structure (II; X = OH) (yield 50%).

EXPERIMENTAL.

(Analytical data quoted in the tables are not repeated below.)

Hexamine Dinitrate–Solvent Reactions. Base A.—(*a*) *Water.* Hexamine dinitrate (100 g.) and water (500 ml.) were refluxed for 1½ hours. The resulting solution was cooled, neutralised with aqueous sodium carbonate, and evaporated to dryness. The residue was extracted with hot methyl alcohol, and the extract cooled. The white needles deposited were recrystallised from alcohol. The nitrate of base *A* had m. p. 192° (6·5 g.).

The methyl-alcoholic filtrate was evaporated yielding a syrup (52 g.), which was dissolved in cold nitric acid (150 ml. of 70%). Methyl alcohol was added carefully, producing a white crystalline precipitate, which was collected, washed with cold ether, and dried in air. This compound, m. p. 140—145° (11 g.), differs from the above nitrate in being insoluble in hot dioxan, acetone, or acetic acid. It gives a strongly acidic solution in water which with the calculated amount of N/10-sodium hydroxide gives the nitrate, m. p. 192—195°, in good yield. The compound, m. p. 142°, is probably 1-methylhexamine 1 : 5-dinitrate (Found : C, 30·1; H, 5·6; N, 30·5; CH_2, 31·1; NO_3^-, 44·5. Calc. for $C_7H_{16}O_6$: C, 30·0; H, 5·7; N, 30·0; CH_2, 30·0; NO_3^-, 44·3%).

The nitrate of base *A* was prepared in better yield as follows. Hexamine dinitrate (25 g.) in water (50 ml.) was refluxed for 2½ hours, and then cooled and evaporated under reduced pressure. The crystalline residue, recrystallised from alcohol, had m. p. 190° (9 g.).

(*b*) *Methyl alcohol.* Hexamine dinitrate (40 g.) was refluxed in methyl alcohol (200 ml.) for 4 hours, evaporated under reduced pressure to 50 ml., and then kept at 0° overnight. The crystals which separated were recrystallised twice from alcohol, giving a nitrate as white needles, m. p. 190° (3·2 g.).

Similar experiments with the dinitrate (40 g.) and ethyl, *iso*propyl, and *tert.*-butyl alcohol gave the nitrate in yields of 3·5 g. (see Table 1).

Salts of Base A (*obtained by hot* H_2O).—*Picrate.* To the nitrate (10 g.) in water (150 ml.), saturated aqueous picric acid was added at 0° until no further precipitation occurred. The orange-red picrate, recrystallised from hot water, had m. p. 208° (12 g.).

Chloride. Prepared as was the corresponding nitrate, starting from hexamine hydrochloride, this was obtained as white needles, m. p. 202° (after softening at 130°, and hardening at 135°) (yield 10—15%). It was also isolated, in good yield, from the filtrate from the precipitation of the nitrate of base *A* by nitron hydrochloride (Found : C, 43·5; H, 8·9; N, 29·8; Cl^-, 18·3. Calc. for $C_7H_{15}N_4Cl$: C, 43·9; H, 7·9; N, 29·4; Cl^-, 18·7%).

Dichromate. Hexamine tetrachromate was prepared by the method of Cambier and Brochet (*Bull. Soc. chim.*, 1895, **13**, 400) by the action of aqueous chromium trioxide on aqueous hexamine. The tetrachromate (42 g.) and water (500 ml.) were heated for 1½ hours on the steam-bath (after the initial dissolution, a dark brown amorphous solid was precipitated). The suspension was cooled and filtered, and the filtrate evaporated to 200 ml. On cooling, orange-yellow crystals separated; when dried, these had m. p. 215° (7 g.) (Found : C, 32·0; H, 6·5; N, 21·1; Cr, 20·0. Calc. for $C_{14}H_{30}O_{14}N_8Cr$: C, 32·0; H, 5·7; N, 21·4; Cr, 20·6%).

Hydroxide. To the chloride (25 g.) in water (150 ml.), moist silver oxide, freshly prepared from silver nitrate (25 g.), was added and the resulting suspension was shaken vigorously for 6 hours at room temperature and then filtered. The filtrate was evaporated under reduced pressure. The oily residue (12 g.), n^{20} 1·4475, of the crude hydroxide was not further purified. The oil is hygroscopic and yields an alkaline solution from which the corresponding picrate can be precipitated in 80% yield.

Salts of Knudsen's Base.—*Nitrate.* This was prepared by a method analogous to that used by Knudsen for the sulphate : a solution of ammonium nitrate (150 g.) in a mixture of aqueous formaldehyde (215 g. of 40%) and water (150 ml.) was heated to 70—80° on a water-bath for 1 hour. The product, isolated as in the case of the nitrate of base *A* and recrystallised from alcohol, had m. p. 190° (12 g.).

Chloride. This was prepared (*a*) by Knudsen's alternative method from pre-formed hexamine, and (*b*) from the nitrate. (*a*) Hexamine (93 g.) was added to a solution of methylamine hydrochloride (90 g.) in hydrochloric acid (229 g.; *d* 1·16) at 20°. The mixture was warmed on a water-bath for ½ hour, and then cooled, neutralised with anhydrous sodium carbonate, and evaporated to dryness. Sodium and ammonium chlorides were removed by extracting the product with hot alcohol (750 ml.). On cooling, the alcoholic extract gave a crop of crystals, mainly methylamine hydrochloride (25 g.) which was collected. Evaporation of the filtrate to 250 ml. gave a mixture (39 g.) of methylamine hydrochloride and Knudsen's chloride. Fractional crystallisation from alcohol gave the chloride, m. p. 202° (8 g.). (*b*) The filtrate from the precipitation of the nitrate from Knudsen's nitrate by nitron hydrochloride was worked up by the usual procedure to give Knudsen's chloride in good yield.

Picrate. This was prepared in 80% yield by addition of picric acid solution to a solution of any of the other salts of Knudsen's base, or the hydroxide.

Hydroxide. This was prepared from the chloride by the method used for base *A*.

Derivatives of 1-*Methylhexamine* (*Hexamine Metho-salts*).—1-*Nitrate.* Hexamine methiodide was prepared by refluxing, for 1 hour, hexamine (35 g.) suspended in methyl alcohol (250 ml.) and methyl iodide (40 g.). The methiodide was treated directly in hot methyl-alcoholic solution with powdered silver nitrate (43 g.). The whole was refluxed for ½ hour, and the resulting suspension was cooled and filtered. The methyl-alcoholic filtrate was worked up as for the nitrate of base *A* prepared by methyl alcohol. The product crystallised in colourless needles, m. p. 190° (40 g.).

1-*Picrate.* This was prepared by adding an equimolecular proportion of picric acid in saturated alcoholic solution at 60° to a solution of authentic hexamine methonitrate in alcohol at 60°. The resulting system was cooled to 0°; the product, hexamine methopicrate, when dried, formed orange-yellow needles, m. p. 210° (85%).

1-*Hydroxide.* This was synthesised from formaldehyde, ammonia, and methylamine as follows. (*a*) Using stoicheiometric proportions of the reagents correct for (III; X = OH). Paraformaldehyde (18 g., 0·6 mol.) was added to a solution of ammonia (17·5 ml., 0·3 mol.; *d* 0·880) and methylamine (9·5 ml., 0·1 mol.; 33%) at room temperature; the paraformaldehyde slowly dissolved, dissolution being accompanied by slight evolution of heat. The solution was kept overnight and then evaporated at 50°/20 mm. The product was extracted with ether, the ethereal solution dried and evaporated, and the product was finally dried *in vacuo* (12 g., 70%). (*b*) Using the stoicheiometric proportions of reagents correct for (II; X = OH), *i.e.*, paraformaldehyde (18 g., 0·6 mol.), ammonia (11 ml., 0·6 mol.; *d* 0·880), and methylamine (19·0 ml., 0·2 mol.; 33%). The yield was 8·5 g. (50%).

The authors acknowledge the assistance of Professor F. J. Llewellyn with the *X*-ray powder photography, helpful discussions with Dr. E. Roberts (E. R. D. E.), Dr. A. Carruthers and Dr. N. H. Woodbury (Bristol), and Dr. F. B. Strauss (Oxford), and extensive private communications from Professor Marvin Carmack (University of Pennsylvania). The authors thank the Chief Scientist of the Ministry of Supply for permission to publish this paper.

THE UNIVERSITY OF MANCHESTER.
EXPLOSIVES RESEARCH AND DEVELOPMENT ESTABLISHMENT,
MINISTRY OF SUPPLY.

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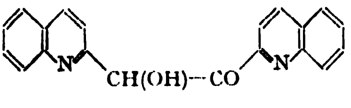
121. *Cyclic Meso-ionic Compounds derived from Quinoline.*

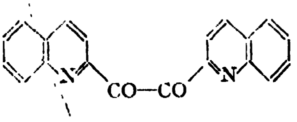
By B. R. BROWN and D. LL. HAMMICK.

A new class of compound, produced by the action of cyanide or cyanide-type ions on aldehydes of the quinoline and *iso*quinoline series, is described. The evidence for regarding them as possessing meso-ionic structures (IV) is reviewed. We propose to call them quinocolls, a systematic name for them being 3 : 6-dihydroxydiquinolino(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)-pyrazinium dihydroxide bisanhydro-salts. A mechanism for their production is suggested.

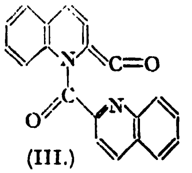
HENZE (*Ber.*, 1934, **67**, 753) reports that quinaldoin (I), m. p. 261°, is produced by the action of aqueous-alcoholic potassium cyanide on quinoline-2-aldehyde. No analysis or chemical properties of the compound are given. Kaplan (*J. Amer. Chem. Soc.*, 1941, **63**, 2654) confirmed this work and recorded an analysis. He also obtained the compound (very pale brown needles, m. p. 269—271°) by the action of old selenium dioxide on quinaldine in dioxan. By analogy with the formation of benzoin from benzaldehyde and potassium cyanide, Kaplan assumed that the compound was quinaldoin (I), but recorded no chemical properties. Later Linsker and Evans (*ibid.*, 1946, **68**, 947) obtained a compound, m. p. 175°, which they formulated as quinaldil (II), from the reaction of selenium dioxide with quinaldine. This reacted with urea in the same way as does benzil, and on reduction yielded a compound, m. p. 135°, which had the chemical properties expected for quinaldoin (I).



(I.)



(II.)



(III.)

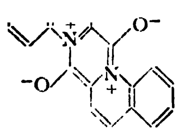
By the decarboxylating action of picolinic or quinaldinic acid on quinoline-2-aldehyde we have obtained a compound in the form of colourless needles, m. p. 266—267°, which proved to be identical with the compound produced from quinoline-2-aldehyde and potassium cyanide. This is a further example of the analogous chemical behaviour of the cyanide ion and the ions resulting from the decarboxylation of picolinic and quinaldinic acids (Dyson and Hammick, *J.*, 1937, 1724; Ashworth, Daffern, and Hammick, *J.*, 1939, 809; Brown and Hammick, *J.*, 1949, 173).

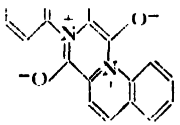
The compound dissolves in concentrated hydrochloric acid and in 30% sulphuric acid to a yellow solution. It forms a yellow *diperchlorate*. Oxidation with potassium permanganate in hot aqueous pyridine yields 77% of quinaldinic acid. The compound reacts vigorously with hot concentrated aqueous potassium hydroxide to yield 60% of potassium quinaldinate. This reaction proceeds with simultaneous reduction of added methylene-blue. Boiling aniline converts the compound into the anilide of quinaldinic acid. The compound is inert towards carbonyl or hydroxyl group reagents under a variety of conditions, and *is* unaffected by cold potassium permanganate solution or by bromine water.

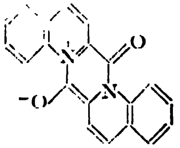
Elementary analysis of the compound agrees better with the empirical formula $C_{20}H_{12}O_2N_2$ than with $C_{20}H_{14}O_2N_2$ [cf. Kaplan (*loc. cit.*) whose analysis also agrees better with $C_{20}H_{12}O_2N_2$].

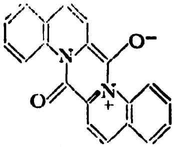
A molecular-weight determination proved impossible owing to insolubility of the compound in suitable solvents. However, a dimethyl analogue produced from *3-methylquinoline-2-aldehyde* and potassium cyanide is more soluble, and a molecular-weight determination in camphor indicates that its molecular formula is $C_{22}H_{16}O_2N_2$, *i.e.*, that it corresponds with a molecular formula of $C_{20}H_{12}O_2N_2$ for the original compound. Thus in its formation from two molecules of quinoline-2-aldehyde two hydrogen atoms must be lost: $2C_{10}H_7ON = C_{20}H_{12}O_2N_2 + 2H$. This was established by the observations that added methylene-blue is reduced and the compound produced when an aqueous-alcoholic solution of quinoline-2-aldehyde is treated with aqueous potassium cyanide.

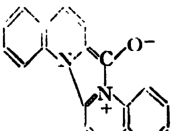
The experiments of Linsker and Evans (*loc. cit.*) together with the chemical evidence which we have obtained (lack of carbonyl or hydroxyl group reactivity) indicate that the compound is neither quinaldoin (I) nor quinaldil (II). Furthermore, Mr. B. H. Thewlis working in this laboratory has independently synthesised quinaldil (II), which is identical with the compound of Linsker and Evans, from 1 : 2-di-2′-quinolylethane. Another possibility, the keten structure (III), is eliminated on account of the stability of the compound towards reagents such as alcohol. The oxidation of the substance to quinaldinic acid necessitates the conclusion that only the α-carbon atoms and possibly the nitrogen atoms are involved in the fusion of the two quinoline nuclei which the molecular weight indicates. The physical properties of the substance (insolubility in common solvents and high m. p.) indicate that it has a salt-like structure. This, together with the fact that the obvious structures have been eliminated, leads us to suggest that the compound has the structure of a zwitterion. A few of the contributing canonical forms, (IV), (V), (VI), and (VII), are shown below. This structure, though revoluntionary, is of the type called " meso-ionic " by Baker, Ollis, and Poole (*J.*, 1949, 307), and is analogous to the formulæ which they have proposed for the sydnones. A much closer parallel is the zwitterion formula (VIII)—(IX), suggested by Krollpfeiffer and Schneider (*Annalen*, 1937, **530**, 34) for Besthorn's red, a compound produced by the decarboxylation of quinaldinic acid in acetic anhydride (Besthorn and Ibele, *Ber.*, 1904, **37**, 1236; 1905, **38**, 2127). Since in the resonance hybrid of the new structure, comprising (IV), (V), (VI), and (VII), there is no actual shift of electronic charge the compound is expected to be colourless. Besthorn's red provides an interesting contrast, since in the molecule of this compound the positive charge is asymmetrically distributed across a conjugated system. On reaction with a strong acid (*e.g.*, sulphuric or perchloric) the compound (IV) can act as a diacidic base yielding a cation capable of formulation in terms of canonical forms such as (X) and (XI). Consequently, on account of the asymmetry and mobility of the positive charge, it is not surprising that this cation is yellow.

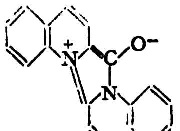

(IV.)

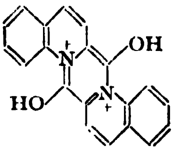

(V.)

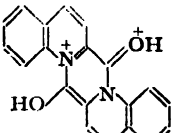

(VI.)


(VII.)

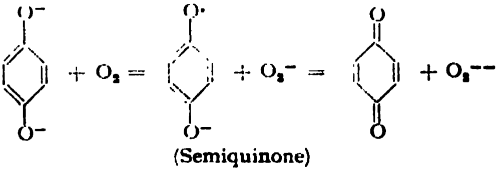

(VIII.)


(IX.)


(X.)

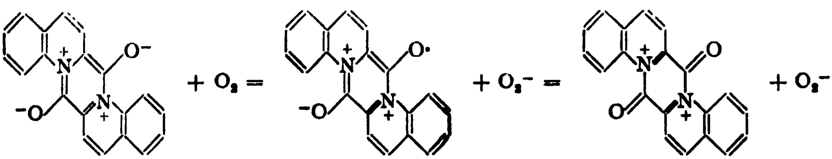

(XI.)

The autoxidation and alkaline hydrolysis of the compound are particularly suggestive of the meso-ionic formula advanced. The structure suggested for the compound is similar to that of a quinol ion, and it is well known (Weissberger, Thomas, and Valle, *J. Amer. Chem. Soc.*, 1943, **65**, 1489) that in alkaline solution quinols readily undergo autoxidation to yield the corresponding quinones :



(Semiquinone)

A similar autoxidation of our compound would proceed as follows :

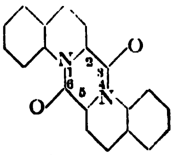


(XII.) (XIII.)

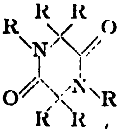
The product (XIII) is the cation of an acylquinolinium hydroxide, and hence would be expected to hydrolyse readily to quinaldinic acid. The formation of a semiquinone type of ion (XII) as an intermediate is suggested by the deep colour which appears and then fades as the reaction with alkali proceeds. The reaction with aniline producing the anilide of quinaldinic acid possibly involves a similar oxidative attack.

We have given the trivial name quinocoll to the structure, by analogy with the compound pyrocoll (XVIII) (Weidel and Ciamician, *Monatsh.*, 1880, **1**, 279; Ciamician and Silber, *Ber.*, 1884, **17**, 106) which has almost the same central ring fused to two pyrrole nuclei. The quinoline rings are numbered in the normal manner, so that the compounds (XXIII) and (XXIV) are respectively 3 : 3′-dimethyl- and 6 : 6′-dimethylquinocoll. We feel that for convenience it is desirable to have such a name, though it is also clearly necessary to have a systematic description. The Editor has suggested that the parent compound (IV) be called 3 : 6-dihydroxydiquinolino-(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)pyrazinium dihydroxide bisanhydro-salt, and that the numbering be as indicated (XIV). Thus the compound is regarded as the internal salt resulting from the dehydration of a phenolic ammonium hydroxide.

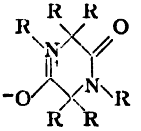
It is of interest to compare the central ring in this new structure with that in the diketopiperazines (XV), (XVI), and (XVII), and in the compound called pyrocoll (XVIII), (XIX), and (XX) (*idem, ibid.*). The difference is to be found in the fact that the new structure is completely aromatic, the central ring containing six non-localised electrons. In the diketopiperazines and in pyrocoll the central ring contains only four non-localised electrons. This difference is reflected in the alkaline hydrolysis of these compounds, pyrocoll yielding pyrrole-2-carboxylic acid directly, but quinocoll undergoing simultaneous autoxidation and hydrolysis to yield quinoline-2-carboxylic acid.



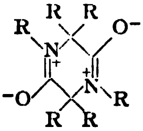
(XIV.)



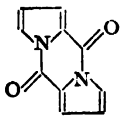
(XV.)



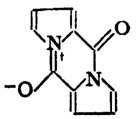
(XVI.)



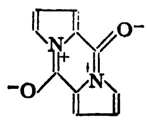
(XVII.)



(XVIII.)

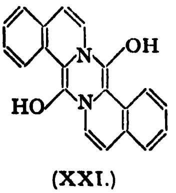


(XIX.)

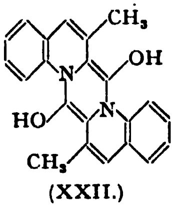


(XX.)

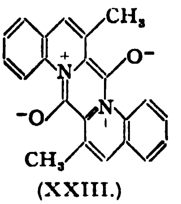
The reaction of quinoline-2- and *iso*quinoline-1-aldehydes with potassium cyanide to yield quinocolls appears to be quite general. Under these conditions *iso*quinoline-1-aldehyde and 3-methylquinoline-2-aldehyde yield the *dihydro*-derivatives (XXI) and (XXII), which exhibit none of the reactions of keto-compounds. Both these compounds are thermochromic, being



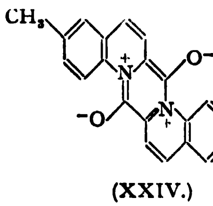
(XXI.)



(XXII.)



(XXIII.)

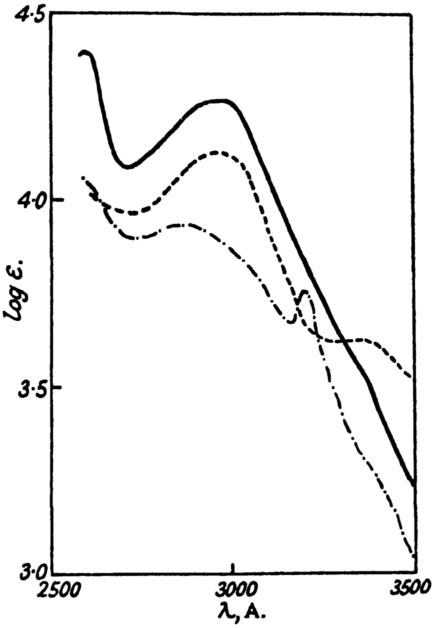


(XXIV.)

colourless in cold alcoholic solution and passing reversibly on being heated through yellow and orange to deep red. Both readily reduce methylene-blue, and (XXII) is oxidised by air to 3 : *3′-dimethylquinocoll* (XXIII). This compound does not readily undergo autoxidation and hydrolysis with alkali, possibly owing to a steric effect of the methyl groups adjacent to the central ring. 6-*Methylquinoline*-2-*aldehyde* reacts with potassium cyanide to yield 6 : *6′-dimethylquinocoll* (XXIV) directly.

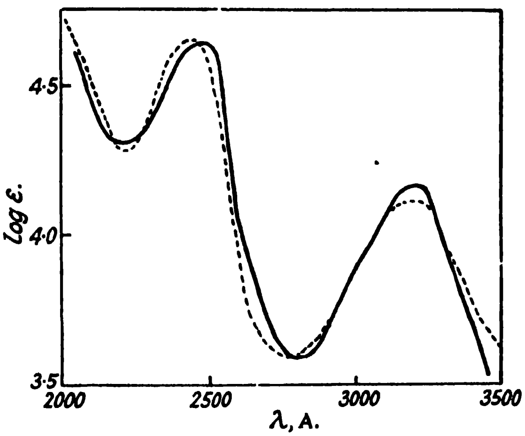
The isolation of dihydro-compounds which are readily oxidised to quinocolls indicates that the formation of the meso-ionic structure occurs by dimerisation of the quinoline-2-aldehyde under the influence of cyanide-type ions, followed by atmospheric oxidation of the resulting dihydro-derivative. The processes involved are illustrated in a simple manner by the following tentative mechanism. An analogy for the initial addition is provided by the reaction between quinoline and benzaldehyde in sunlight, which yields 1-benzoyl-1 : 2-dihydroquinoline (Benrath, *J. pr. Chem.*, 1906, **73**, 384).

FIG. 1.

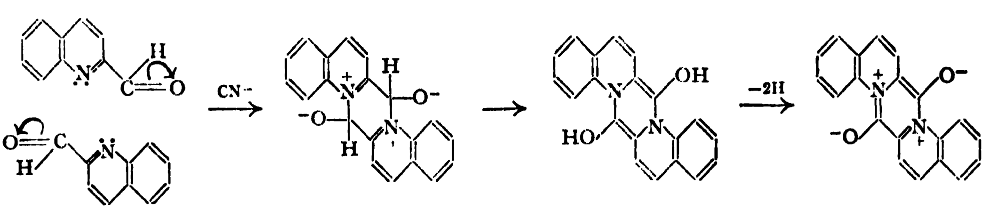


——— *Absorption spectrum of quinocoll in dioxan.*
- - - - *Absorption spectrum of* 3 : 3′-*dimethylquinocoll in dioxan.*
—·—· *Absorption spectrum of* 3 : 3′-*dimethyldihydroquinocoll in dioxan.*

FIG. 2.



——— *Absorption spectrum of quinocoll in* 30% *sulphuric acid.*
- - - - *Absorption spectrum of* 3 : 3′-*dimethylquinocoll in* 30% *sulphuric acid.*



The ultra-violet absorption spectra of quinocoll and its 3 : 3′-dimethyl analogue in dioxan and in 30% sulphuric acid (Figs. 1 and 2) leave little doubt that the compounds have analogous structures. The spectrum of 3 : 3′-dimethyldihydroquinocoll in dioxan (Fig. 1) is very similar to those of ordinary quinoline derivatives, and differs markedly from the spectra of the quinocolls.

EXPERIMENTAL.

(M. p.s are uncorrected. Analyses are by Mr. F. C. Hall. Absorption spectra are by Dr. F. B. Strauss of Oxford.)

ωω-Dibromoquinaldine *.—ωωω-Tribromoquinaldine (48·0 g.) was heated in tetralin (80 ml.) at 100° for 12 hours. The resulting brown crystalline mass was diluted with light petroleum, and the light-brown crystals (34·4 g.) were recrystallised from alcohol. ωω-Dibromoquinaldine was obtained as colourless needles, m. p. 119—120°. Hammick (*J.*, 1926, 1302) records m. p. 120°.

Quinocoll [3 : 6-*Dihydroxydiquinolino*(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)*pyrazinium Dihydroxide Bisanhydro-salt*] (IV).—(a) *By the action of potassium cyanide on quinoline-2-aldehyde* (Henze, *loc. cit.*; Kaplan, *loc. cit.*). The compound separated from pyridine as pale yellow needles, m. p. 266—267°. After treatment of a hot pyridine solution with a drop of acetic anhydride the compound crystallised as colourless needles, m. p. 266—267°. Henze (*loc. cit.*) gives m. p. 261°; Kaplan (*loc. cit.*) gives m. p. 269—271°.

(b) *By the decarboxylation of picolinic or quinaldinic acid in quinoline-2-aldehyde.* A mixture of picolinic or quinaldinic acid (0·2 g.) and quinoline-2-aldehyde (1·0 g.) was heated at 150—165° for 10 minutes. Carbon dioxide was evolved and a vigorous reaction occurred, during which the mixture darkened and completely solidified. The mass of dark brown needles was collected, washed with alcohol, and recrystallised several times from pyridine (plus a drop of acetic anhydride to remove the colour). The compound (0·7 g.) was thus obtained as colourless needles, m. p. 266—267°, unchanged on admixture with the compound obtained from the action of potassium cyanide on quinoline-2-aldehyde (Found: C, 76·9; H, 4·0; N, 9·2. Calc. for $C_{20}H_{12}O_2N_2$: C, 76·9; H, 3·85; N, 9·0%). The compound is slightly soluble in hot ethyl alcohol, glacial acetic acid, benzene, or chloroform, but almost insoluble in water, acetone, or light petroleum. It crystallises well from dioxan or from 2-methoxyethanol. It is soluble in concentrated hydrochloric or sulphuric acid with production of a yellow colour. It is insoluble in cold dilute alkalis.

The compound is unaffected under a variety of conditions by acetic anhydride, acetyl chloride, benzoyl chloride, phenylhydrazine, 2 : 4-dinitrophenylhydrazine, or bromine. It forms no picrate.

The *perchlorate* separated from a mixture of acetic and 60% perchloric acid as small yellow prisms, m. p. (rapid heating) 222—223° (decomp.), which were dried at 50° in a vacuum (Found: Cl, 14·4. $C_{20}H_{12}O_2N_2,2HClO_4$ requires Cl, 13·8%).

Permanganate Oxidation of Quinocoll.—A solution of quinocoll (0·5 g.) in a mixture of pyridine and water (20 ml. each) was treated at 90° during 2 hours with potassium permanganate (2·0 g.) in water (10 ml.). The precipitated manganese dioxide was collected and washed with hot water, and the colourless filtrate made just acid and again filtered. Treatment with excess of copper sulphate solution yielded a greyish-blue precipitate of copper quinaldinate, which was washed with hot water and dried at 100° (0·5 g., 77%). The copper salt was converted into the crystalline sodium salt from which the hydrochloride of quinaldinic acid was obtained as colourless needles (from alcohol), m. p. 192—196° (decomp.).

Autoxidation and Alkaline Hydrolysis of Quinocoll.—Quinocoll (0·5 g.) in hot dioxan (20 ml.) was treated with a solution of potassium hydroxide (2·0 g.) in water (3 ml.). A vigorous reaction occurred and the solution became dark brown. The mixture was boiled under reflux for 30 minutes, during which the colour faded appreciably. The aqueous layer of potassium hydroxide was separated and proved to contain no potassium quinaldinate. The dioxan layer was evaporated under reduced pressure, and the resulting potassium quinaldinate (0·4 g., 60%) converted into the hydrochloride of quinaldinic acid, m. p. 189—194° (decomp.).

Action of Aniline on Quinocoll.—Quinocoll (0·5 g.) was heated under reflux with redistilled aniline (15 ml.) for 4 hours. Initially the solution became very dark brown, but finally it had a clear yellowish-brown colour. Distillation with steam removed aniline, and on cooling the residual brown oil solidified. Two crystallisations from alcohol yielded colourless silky needles (0·4 g., 50%), m. p. 138—139° (Found: C, 77·7; H, 4·8; N, 11·0. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·8; N, 11·3%). On admixture with an authentic specimen of the anilide of quinaldinic acid (Krollpfeiffer and Schneider, *loc. cit.*) the m. p. was unchanged.

3-*Methylquinoline-2-aldehyde.*—β-(3-Methyl-2-quinolyl)acrylic acid (16·0 g.) (Brown, Hammick, and Robinson, *J.*, in the press), sodium carbonate solution (150 ml. of 6%), and benzene (100 ml.) were cooled in ice, stirred vigorously, and treated during 1 hour with powdered potassium permanganate (25·3 g.). The mixture was filtered, the manganese dioxide washed with ether, and the ether–benzene layer separated from the filtrate, washed with water, and dried. Removal of the solvents yielded 3-*methylquinoline-2-aldehyde* (6·8 g.) as a slightly yellow crystalline solid. Recrystallisation from light petroleum (b. p. 80—100°) gave flat colourless needles, m. p. 114—115° (Found: C, 77·1; H, 5·3. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%). The 2 : 4-*dinitrophenylhydrazone* separated from xylene–pyridine as fine orange-coloured needles, m. p. 261—262° (Found: N, 19·7. $C_{17}H_{13}O_4N_5$ requires N, 19·9%).

3 : 3′-*Dimethyldihydroquinocoll* (XXII). *Action of Potassium Cyanide on* 3-*Methylquinoline*-2-*aldehyde.*—A hot solution of 3-methylquinoline-2-aldehyde (1·5 g.) in alcohol (15 ml.) and water (15 ml.) was treated under nitrogen with a solution of potassium cyanide (0·2 g.). The solution immediately became dark brown and a crystalline solid separated. Several recrystallisations from alcohol yielded 3 : 3′-*dimethyldihydroquinocoll* (0·9 g.) as colourless rectangular prisms, m. p. 154—155° to a dark red melt (Found: C, 77·65; H, 5·45. $C_{22}H_{18}O_2N_2$ requires C, 77·2; H, 5·3%). The compound is thermochromic. Its cold alcoholic solution is colourless, but on being heated it passes slowly through yellow and orange to deep red. These colour changes are reversed as the solution cools. The compound is soluble in acids but not in alkalis. In air it slowly becomes light brown and falls to a powder. A hot alcoholic solution of the dihydro-compound quickly reduces and decolorises methylene-blue. It does not react with phenylhydrazine.

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* The free-radical mechanism of this reaction will be discussed in a later publication.

3 : 3′-*Dimethylquinocoll* [3 : 6-*Dihydroxy*-3′ : 3″-*dimethyldiquinolino*(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)-*pyrazinium Dihydroxide Bisanhydro-salt*] (XXIII).—When 3 : 3′-dimethyldihydroquinocoll is kept in air for several days the colourless rectangular prisms gradually change into a light-brown powder, which is only very slightly soluble in boiling alcohol. Recrystallisation from alcohol–pyridine yields 3 : 3′-*dimethylquinocoll* as slightly brown needles, m. p. 220—221° [Found : C, 77·4; H, 4·8%; *M* (cryoscopic in camphor), 330. $C_{22}H_{16}O_2N_2$ requires C, 77·65; H, 4·7%; *M*, 340]. The compound is readily soluble in cold pyridine or dioxan. Its solution in propyl alcohol yields no colour or precipitate with 2 : 4-dinitrophenylhydrazine sulphate.

6-*Methyl-2-tribromomethylquinoline*.—Bromination of 2 : 6-dimethylquinoline (35·0 g.) (Doebner and Miller, *Ber.*, 1883, **16**, 2465) by the method of Hammick (*J.*, 1923, 2882) yielded 6-*methyl-2-tribromomethylquinoline* (54·7 g.), which separated from acetic acid as colourless narrow plates, m. p. 132—133° (Found : Br, 61·0. $C_{11}H_8NBr_3$ requires Br, 60·9%).

6-*Methyl-2-dibromomethylquinoline*.—The above tribromo-compound (50·0 g.) was heated at 100° with tetralin (85 ml.) for 12 hours. The mixture was diluted with light petroleum (b. p. 40—60°) and kept at 0° overnight. The light-brown crystals (24·9 g.) were recrystallised from alcohol. 6-*Methyl-2-dibromomethylquinoline* was thus obtained as colourless needles, m. p. 85—86° (Found : Br, 51·0. $C_{11}H_9NBr_2$ requires Br, 50·8%).

6-*Methylquinoline-2-aldehyde*.—6-Methyl-2-dibromomethylquinoline (6·0 g.) was hydrolysed by means of silver nitrate (method of Hammick, *J.*, 1926, 1302). Steam-distillation from slightly alkaline solution yielded a colourless oil which solidified in the distillate. The *aldehyde* (2·7 g.), which was isolated by means of ether, separated from light petroleum (b. p. 40—60°) as colourless elongated plates, m. p. 105—106° (Found : C, 77·5; H, 5·3. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%).

6 : 6′-*Dimethylquinocoll* [3 : 6-*Dihydroxy*-6′ : 6″-*dimethyldiquinolino*(1′ : 2′-1 : 2)(1″ : 2″-4 : 5)-*pyrazinium Dihydroxide Bisanhydro-salt*] (XXIV).—6-Methylquinoline-2-aldehyde (1·7 g.) was treated in hot aqueous alcohol with an aqueous solution of potassium cyanide (0·2 g.), and the mixture heated under reflux for 15 minutes. The reddish-brown precipitate was collected, washed with water, and crystallised several times from pyridine or dioxan. 6 : 6′-*Dimethylquinocoll* was obtained as small slightly yellow plates, m. p. 250—251° (Found : C, 77·8; H, 4·9. $C_{22}H_{16}O_2N_2$ requires C, 77·65; H, 4·7%).

*Dihydro*iso*quinocoll* (XXI). *Action of Potassium Cyanide on* iso*Quinoline*-1-*aldehyde*.—A hot solution of *iso*quinoline-1-aldehyde (1·0 g.) (Barrows and Lindwall, *J. Amer. Chem. Soc.*, 1942, **64**, 2430) in aqueous alcohol (50 ml.) was treated with an aqueous solution of potassium cyanide (0·2 g.) and heated under reflux for 15 minutes. The mixture was cooled and the brown crystals (1·0 g.) were collected, washed, and dried. Several recrystallisations from alcohol yielded *dihydro*iso*quinocoll* as fine slightly brown needles, m. p. 163—164° to a dark red melt (Found : C, 76·5; H, 4·65; N, 8·9. $C_{20}H_{14}O_2N_2$ requires C, 76·4; H, 4·45; N, 8·9%). The compound shows thermochromism, its alcoholic solution passing reversibly on being heated through yellow and orange to deep red. The compound quickly reduces methylene-blue in aqueous alcohol. It yields no hydrazone with 2 : 4-dinitrophenylhydrazine sulphate in alcohol.

We thank Dr. H. M. E. Cardwell for much helpful discussion.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 5th, 1949.*]

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122. *Studies in the Polyene Series. Part XXXVI. Further Syntheses of Acetylenic Acids related to Vitamin A.*

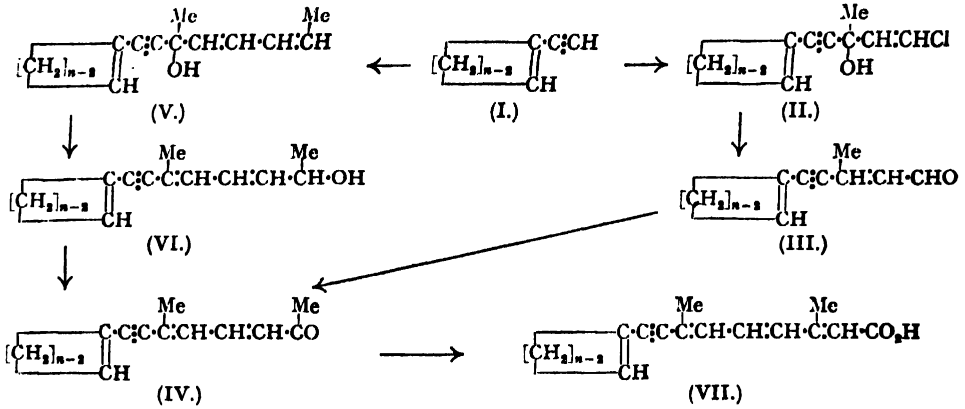
By T. BRUUN, SIR IAN HEILBRON, B. C. L. WEEDON, and R. J. WOODS.

Methods previously developed for the preparation of the *cyclo*hexenyl acid (VII; *n* = 6), which possessed slight growth-promoting properties of the vitamin-A type, have now been applied to the synthesis of the *cyclo*pentenyl and *cyclo*heptenyl analogues (VII; *n* = 5 and 7), both of which were found to be biologically inactive.

As part of a general scheme for the synthesis of compounds with modified vitamin-A structures, the *cyclo*pentenyl and *cyclo*heptenyl acids (VII; *n* = 5 and 7) have now been prepared by the methods previously developed (Heilbron, Jones, and Richardson, *J.*, 1949, 287; Toogood and Weedon, *J.*, 1949, 3123) for the synthesis of the acid (VII; *n* = 6). The last was shown to possess slight but definite growth-promoting properties of the vitamin-A type, and it appeared of interest to examine the effect of varying the size of the ring system on biological activity.

The Grignard reagents from ethynyl*cyclo*pentene (I; *n* = 5) and ethynyl*cyclo*heptene (I; *n* = 7) (Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 1827) were condensed with methyl 2-chlorovinyl ketone and gave the *carbinols* (II; *n* = 5 and 7) in 70 and 90% yields, respectively. The latter on treatment with dilute sulphuric acid underwent anionotropic rearrangement and simultaneous loss of hydrogen chloride, yielding the *aldehydes* (III; *n* = 5 and 7) which were converted into the *ketones* (IV; *n* = 5 and 7) by condensation with acetone in the presence of aluminium *tert.*-butoxide.

The same ketones were also synthesised by the following route. The *carbinols* (V; *n* = 5 and 7), prepared in 65 and 60% yields, respectively, by reaction of the Grignard reagents from (I; $n = 5$ and 7) with crotonylideneacetone, were isomerised by being shaken with dilute sulphuric acid to the fully conjugated *carbinols* (VI; $n = 5$ and 7). Oppenauer oxidation of the latter furnished the ketones (IV; $n = 5$ and 7), identical with those obtained by the alternative route described above.



Condensation of the ketones (IV; $n = 5$ and 7) with methyl bromoacetate and zinc gave, after dehydration of the crude hydroxy-esters and hydrolysis, the crystalline *acids* (VII; $n = 5$ and 7), in 11 and 7% yields, respectively. Neither of these acids showed any growth-promoting properties when fed orally, as aqueous solutions of the sodium salts buffered to pH 10, to young rats deficient in vitamin A [the doses administered would have revealed activity of the same order as that of (VII; $n = 6$), *viz.*, one-thousandth of that of vitamin A itself].

The various compounds described in this paper all exhibited light-absorption properties similar to those of the corresponding *cyclo*hexenyl analogues (see table).

		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Carbinol	(II; $n = 5$)	2290	12,000
	(II; $n = 6$)[1]	2290	13,000
	(II; $n = 7$)	2320	17,000
		2380 *	15,500
Aldehyde	(III; $n = 5$)	2270	15,500
		3110	14,500
	(III; $n = 6$)[1]	2230	14,000
		2810	10,500
		3140	14,000
	(III; $n = 7$)	2260	13,000
		3160	14,500
Ketone	(IV; $n = 5$)	2440	14,500
		3380	28,000
	(IV; $n = 6$)[2]	2450	18,000
		3350	23,000
	(IV; $n = 7$)	2450	13,500
		3350	20,000
Carbinol	(V; $n = 5$)	2280	34,500
		2390 *	27,000
	(V; $n = 6$)[2]	2270	39,000
		2370	30,000
	(V; $n = 7$)	2290	33,000
		2400 *	26,500
Carbinol	(VI; $n = 5$)	2260	16,500
		2830 *	21,500
		2930	23,500
		3000 *	21,500
		3080	19,000
	(VI; $n = 6$)[2]	2910	21,500
		3060	15,000
	(VI; $n = 7$)	2980	27,000
		3070 *	22,000
Acid	(VII; $n = 5$)	2600	18,000
		3400	36,000
	(VII; $n = 6$)[3]	2580	14,000
		3380	33,000
	(VII; $n = 7$)	2580	13,500
		2640	15,500
		3410	34,000

* Inflexion.

[1] Toogood and Weedon, *loc. cit.* [2] Heilbron, Jones, and Richardson, *loc. cit.* [3] Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823.

EXPERIMENTAL.

Light-absorption data were determined in alcohol unless stated otherwise: those not referred to below are to be found in the table. All the operations were carried out in an atmosphere of nitrogen. The 2 : 4-dinitrophenylhydrazones were purified by chromatographic adsorption on alumina from benzene solution.

1-*Chloro*-5-cyclo*pent*-1′-*enyl*-3-*methylpent*-1-*en*-4-*yn*-3-*ol* (II; $n = 5$).—Ethynyl*cyclo*pentene (21 g.) (Heilbron, Jones, Toogood, and Weedon, *loc. cit.*) in ether (50 c.c.) was added dropwise to a solution of ethylmagnesium bromide (from 5·6 g. of magnesium) in ether (100 c.c.), and the mixture was refluxed for 4 hours. After cooling, a solution of methyl 2-chlorovinyl ketone (Catch, Elliott, Hey, and Jones, *J.*, 1948, 278) (15·9 g.; freshly prepared) in ether (50 c.c.) was added during ½ hour and the mixture was refluxed for 1 hour and then cooled. The Grignard complex was decomposed with ice and ammonium chloride (20 g.) and the product was isolated with ether. Distillation gave the *carbinol* (20·9 g.) as a pale yellow viscous liquid, b. p. 65—70° (bath temp.)/10^{-4} mm., n_D^{15} 1·5398 (Found: C, 67·45; H, 6·85. $C_{11}H_{13}OCl$ requires C, 67·15; H, 6·65%).

5-cyclo*Pent*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (III; $n = 5$).—The above chloro-carbinol (26 g.) was divided into two equal portions and each was added to dilute sulphuric acid (1·5 l.; 1% w/v), and the mixtures steam-distilled. The distillates were combined and the product was isolated by ether extraction. Evaporation of the ethereal solution gave the crude aldehyde (14·7 g.) as a yellow oil, n_D^{14} 1·5791. Light absorption: maxima, 3080 and 3170 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 780 and 750, respectively, indicating a purity of *ca.* 80%. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate–methanol in dark red needles, m. p. 164—165° (Found: N, 16·7. $C_{17}H_{16}O_4N_4$ requires N, 16·45%). Light absorption in chloroform (main band only): maximum, 3940 A.; ε, 36,000.

The crude aldehyde (5 g.) was treated with an excess of semicarbazide acetate in aqueous methanol (80%) and gave the *semicarbazone* (2·5 g.), which crystallised from alcohol in plates, m. p. 206—207° (decomp.) (Found: N, 19·3. $C_{12}H_{15}ON_3$ requires N, 19·35%). Light absorption: maxima, 2450 and 3160 A.; ε, 11,500 and 30,500, respectively. Inflexion, 3300 A.; ε, 21,000. A mixture of the semicarbazone (1·6 g.), dilute sulphuric acid (50 c.c.; 10% w/v), and light petroleum (50 c.c.; b. p. 80—100°) was refluxed with vigorous stirring for 4 hours. After removal of unreacted semicarbazone (0·8 g.), the petroleum layer was separated, washed with water, dried, and evaporated. Distillation of the residue gave 5-cyclo*pent*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (0·3 g.) as a yellow viscous liquid, b. p. 60° (bath temp.)/10^{-4} mm., n_D^{20} 1·5830, which crystallised when kept at 0° (Found: C, 83·0; H, 7·85. $C_{11}H_{12}O$ requires C, 82·45; H, 7·55%).

1-cyclo*Pent*-1′-*enyl*-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (V; $n = 5$).—Crotonylideneacetone (14·4 g.) in ether (20 c.c.) was added during 1 hour to a cooled suspension of *cyclo*pentenylethynylmagnesium bromide (prepared as described above from 3·2 g. of magnesium and 12·1 g. of ethynyl*cyclo*pentene) in ether (500 c.c.). After the mixture had been stirred at 20° for 1 hour, the complex was decomposed by addition of ice and ammonium chloride (20 g.). Isolation gave the *carbinol* (17·3 g.) as a pale yellow liquid, b. p. 75—80° (bath temp.)/10^{-4} mm., n_D^{18} 1·5465 (Found: C, 83·1; H, 9·0. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

8-cyclo*Pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (VI; $n = 5$).—A mixture of the carbinol (V; $n = 5$) (4·8 g.), dilute sulphuric acid (250 c.c.; 1% w/v), ether (50 c.c.), and a trace of quinol was shaken at 20° for 18 hours. The ethereal layer was separated, washed well with water, dried, and evaporated. Distillation of the residue gave the rearranged *carbinol* (2·3 g.) as a yellow oil, b. p. 80—85° (bath temp.)/10^{-4} mm., n_D^{18} 1·5882 (Found: C, 82·85; H, 9·1. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

8-cyclo*Pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (IV; $n = 5$).—(*a*) A solution of the aldehyde (III; $n = 5$) (14·7 g.; crude) and aluminium *tert.*-butoxide (20·6 g.) in a mixture of acetone (400 c.c.) and benzene (675 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (1200 c.c.; 2·5% w/v), and the organic layer separated. The aqueous solution was extracted with ether and the combined ethereal extracts and benzene layer was washed with sodium hydrogen carbonate solution and water and dried. Evaporation of the solvents and distillation of the residue (9·3 g.) gave the crude ketone (5·5 g.), b. p. 85—90° (bath temp.) 10^{-4} mm., n_D^{15} 1·6064. Light absorption: maxima, 2400 and 3300 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 470 and 800, respectively. Inflexion, 3480 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 680, indicating a purity of *ca.* 45—50%. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in needles and pyramids, m. p. 218—219°. The former were converted into the latter on keeping in contact with solvent and on heating (Found: N, 14·85. $C_{20}H_{20}O_4N_4$ requires N, 14·75%). Light absorption in chloroform (main band only): maximum, 4050 A.; ε, 47,500.

The crude ketone (0·6 g.) was treated with an excess of semicarbazide acetate in aqueous methanol and gave the *semicarbazone* (0·26 g.), which crystallised from methanol in needles, m. p. 169—170° (decomp.) (Found: N, 16·15. $C_{15}H_{19}ON_3$ requires N, 16·35%). Light absorption: maxima, 2640 and 3330 A.; ε, 16,500 and 47,000, respectively. A mixture of the semicarbazone (0·4 g.), dilute sulphuric acid (20 c.c.; 10% w/v), and light petroleum (20 c.c.; b. p. 80—100°) was refluxed with vigorous stirring until all the solid had disappeared (15 minutes). Isolation gave 8-cyclo*pent*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (0·17 g.) as a yellow viscous oil, b. p. 70° (bath temp.)/10^{-4} mm., n_D^{19} 1·6179, which crystallised when kept at 0° (Found: C, 84·05; H, 8·4. $C_{14}H_{16}O$ requires C, 83·95; H, 8·05%).

(*b*) A solution of the carbinol (VI; $n = 5$) (1·4 g.) and aluminium *tert.*-butoxide (4 g.) in a mixture of benzene (10 c.c.) and acetone (60 c.c.) was refluxed for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (460 c.c.; 2·5% w/v), and the product isolated. Distillation gave the crude ketone (1·1 g.), n_D^{22} 1·5920. Light absorption: maxima, 2280, 2420, 3330, and 3380 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 550, 550, 710, and 680, respectively. Inflexion, 3200 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 680. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in needles and pyramids, m. p. 218—219°, undepressed on admixture with a specimen from (*a*). The semicarbazone crystallised from methanol in needles, m. p. 169—170° (decomp.), undepressed on admixture with a specimen from (*a*).

8-cyclo*Pent*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VII; $n = 5$).—A mixture of the ketone (IV, $n = 5$) [4 g.; crude, from (*a*)], methyl bromoacetate (3·5 g.), activated zinc turnings (1·3 g.), a trace of mercuric chloride, and benzene (70 c.c.) was refluxed for ½ hour, all the zinc having then dissolved. The deep-red mixture was cooled and shaken with dilute acetic acid (125 c.c.; 5%). The benzene layer was washed free from acid, dried, and evaporated, giving a mixture (4·5 g.) of hydroxy- and unsaturated esters. Light absorption: maxima, 2820 and 2920 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 620 and 620. Inflexion, 3000 A.; $E^{1\%}_{1\,\mathrm{cm.}}$, 530. Anhydrous oxalic acid (15 g.) was added and the mixture was heated at 95—100° (bath temp.)/10·1 mm. for 2 hours. After cooling, the crude unsaturated ester was isolated by extraction with light petroleum (b. p. 40—60°). Light absorption: maxima, 2600 and 3450 A.; $E^{1\%}_{1\,\text{cm.}}$, 370 and 800, respectively.

The ester was dissolved in methanolic potassium hydroxide (150 c.c.; 10% w/v), and the solution kept at 20° for 64 hours. The solution was poured into water (500 c.c.), the non-hydrolysable material extracted with ether, and the aqueous layer acidified with phosphoric acid (50 c.c.; 50% w/v). The liberated acid was extracted with ether and the ethereal solution was washed with water, dried, and evaporated. Recrystallisation of the residue from methanol gave the *acid* (270 mg.), m. p. 185—186° (Found: C, 79·5; H, 8·0. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

1-*Chloro*-5-cyclo*hept*-1′-*enyl*-3-*methylpent*-1-*en*-4-*yn*-3-*ol* (II; *n* = 7).—Ethynyl*cyclo*heptene (24 g.) (*loc. cit.*) was condensed with methyl 2-chlorovinyl ketone (11·5 g.) by the procedure described above for the *cyclo*pentenyl analogue. Distillation of the product gave: (i) recovered ethynyly*cyclo*heptene (8·5 g.); (ii) the *carbinol* (21 g.) as a pale yellow viscous oil, b. p. 80—85° (bath temp.)/10^{-4} mm., n_D^{18} 1·5372 (Found: C, 69·05; H, 7·7. $C_{13}H_{17}OCl$ requires C, 69·5; H, 7·6%).

5-cyclo*Hept*-1′-*enyl*-3-*methylpent*-2-*en*-4-*yn*-1-*al* (III; *n* = 7).—The chloro-carbinol (II; *n* = 7) (20 g.) was divided into two equal portions and each was added to dilute sulphuric acid (1 l.; 1% w/v) and the mixtures steam distilled. The distillates were combined and the product was isolated with ether and distilled, giving the crude aldehyde (10 g.), b. p. 80° (bath temp.)/10^{-4} mm., n_D^{18} 1·5716. Light absorption: maxima, 2270 and 3150 A.; $E^{1\%}_{1\,\text{cm.}}$, 580 and 560, respectively, indicating a purity of *ca.* 70%. The *semicarbazone* crystallised from methanol in plates, m. p. 205° (Found: N, 17·0. $C_{14}H_{19}ON_3$ requires N, 17·1%). Light absorption: maxima, 2410 and 3170 A.; ε, 12,500 and 29,500, respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from light petroleum (b. p. 60—80°) in dark-red plates, m. p. 156° (Found: N, 15·4. $C_{19}H_{20}O_4N_4$ requires N, 15·2%). Light absorption in chloroform (main band only): maximum, 3980 A.; ε, 39,000.

A mixture of the semicarbazone (1 g.), dilute sulphuric acid (30 c.c.; 10% w/v), and light petroleum (30 c.c.; b. p. 80—100°) was stirred vigorously under reflux until all the solid had disappeared (5 hours). Isolation of the product gave the *aldehyde* (0·5 g.) as a pale yellow oil, b. p. 80° (bath temp.)/10^{-4} mm., n_D^{20} 1·5700 (Found: C, 82·7; H, 9·15. $C_{13}H_{16}O$ requires C, 82·9; H, 8·55%).

1-cyclo*Hept*-1′-*enyl*-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (V; *n* = 7).—Crotonylideneacetone (14·5 g.) in ether (25 c.c.) was added during ½ hour to a cooled suspension of *cyclo*heptenylethynylmagnesium bromide (prepared from 3·0 g. of magnesium and 15·0 g. of ethynyl*cyclo*heptene) in ether (500 c.c.). After the mixture had been stirred at 20° for 1 hour, the complex was decomposed and the product was isolated and distilled, giving the *carbinol* (18·0 g.), b. p. 85—95° (bath temp.)/10^{-4} mm., n_D^{21} 1·5430 (Found: C, 83·45; H, 10·0. $C_{16}H_{22}O$ requires C, 83·45; H, 9·6%).

8-cyclo*Hept*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (VI; *n* = 7).—A solution of the preceding carbinol (15·0 g.), and a trace of quinol, in ether (50 c.c.) was shaken for 15 hours with dilute sulphuric acid (900 c.c.; 0·5% w/v). Isolation of the product gave the crude carbinol. Distillation, which was accompanied by extensive polymerisation, yielded the *carbinol* (8·0 g.) as a viscous pale yellow oil, b. p. 90—100° (bath temp.)/10^{-5} mm., n_D^{18} 1·5800 (Found: C, 83·4; H, 9·9. $C_{16}H_{22}O$ requires C, 83·45; H, 9·6%).

8-cyclo*Hept*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (IV; *n* = 7).—(*a*) A solution of the aldehyde (III; *n* = 7) (18 g.; crude) and aluminium *tert.*-butoxide (25 g.) in a mixture of benzene (800 c.c.) and acetone (400 c.c.) was refluxed for 48 hours. Isolation of the product and distillation gave the ketone (14 g.) as an oil, b. p. 100—110° (bath temp.)/10^{-4} mm., n_D^{24} 1·5920. Light absorption: maxima, 2280, 2370, 2800, and 3300 A.; $E^{1\%}_{1\,\text{cm.}}$, 510, 620, 420, and 770, respectively, indicating a purity of *ca.* 85—90%. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark-red plates, m. p. 200° (Found: N, 13·8. $C_{22}H_{24}O_4N_4$ requires N, 13·7%). Light absorption in chloroform (main band only): maximum, 4080 A.; ε, 36,000. The *semicarbazone*, which formed slowly and in poor yield, crystallised from ethanol in pale yellow needles, m. p. 181° (Found: C, 71·55; H, 8·1. $C_{17}H_{23}ON_3$ requires C, 71·55; H, 8·1%). Light absorption: maximum, 3360 A.; ε, 42,500. Inflexion, 3480 A.; ε, 31,500.

A portion (0·8 g.) of the crude ketone was dissolved in light petroleum (b. p. 40—60°) and the solution was poured on a column of partially deactivated alumina (100 g.; Grade IV, cf. Brockmann and Schodder, *Ber.*, 1941, **74**, 73). The chromatogram was developed with the same solvent and the yellow band formed was eluted and collected in two fractions. Removal of the solvent under reduced pressure and distillation of the residues gave: (i) (least strongly adsorbed) an oil (0·35 g.), b. p. 110—120° (bath temp.)/10^{-4} mm., n_D^{22} 1·5920, and (ii) the *ketone* (0·4 g.) as a pale yellow oil, b. p. 110—120° (bath temp.)/10^{-4} mm., n_D^{19} 1·6132 (Found: C, 84·2; H, 9·2. $C_{16}H_{20}O$ requires C, 84·15; H, 8·85%).

(*b*) A solution of the carbinol (VI; *n* = 7) (9·0 g.) and aluminium *tert.*-butoxide (12·5 g.) in a mixture of acetone (250 c.c.) and benzene (420 c.c.) was refluxed for 48 hours. Isolation gave the crude ketone (7·0 g.) as a pale yellow oil, b. p. 100—110° (bath temp.)/10^{-4} mm.; n_D^{21} 1·5840. Light absorption: maxima, 2450, 3160, and 3370 A.; $E^{1\%}_{1\,\text{cm.}}$, 560, 720, and 720, respectively, indicating an appreciable content of the required ketone.

A solution of the crude ketone (7·0 g.) and Girard reagent-T (7·0 g.) in acetic acid (7·5 c.c.) and alcohol (70 c.c.) was refluxed for 1 hour. Distillation of the crude ketonic material isolated in the usual manner gave the ketone (4 g.), b. p. 90—100° (bath temp.)/10^{-4} mm., n_D^{17} 1·6059. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark red plates, m. p. 199°, undepressed on admixture with a specimen from (*a*). The semicarbazone, which formed slowly and in poor yield, crystallised from methanol in needles, m. p. 179°, undepressed on admixture with a specimen from (*a*).

8-cyclo*Hept*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VII; *n* = 7).—The ketone (IV; *n* = 7) [6·0 g. crude, prepared by route (*a*) above] in benzene (120 c.c.) was condensed with ethyl bromoacetate (5·3 g.) and zinc (1·9 g.). The resulting crude hydroxy-ester was dehydrated, giving the crude unsaturated ester (8·5 g.), n_D^{22} 1·572. Light absorption: maxima, 2490, 2800, and 3420 A.; $E^{1\%}_{1\,\text{cm.}}$, 540, 370, and 680, respectively.

The unsaturated ester was dissolved in a solution of potassium hydroxide in methanol (250 c.c.;

10% w/v), and the solution kept at 20° for 96 hours. Isolation of the acid fraction yielded a viscous yellow gum which partly solidified on trituration with ether. Recrystallisation of the solid from methanol gave the *acid* (0·5 g.) as needles, m. p. 181° (Found: C, 79·8; H, 8·55. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%).

A sample of the ketone (IV; *n* = 7), prepared by route (*b*) above, was also converted into the acid, which crystallised from methanol in needles, m. p. 181°, undepressed on admixture with the specimen described above.

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Imperial College of Science and Technology,
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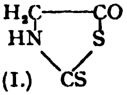
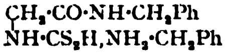
123. *Studies in the Azole Series. Part XXV. The Action of Bases on 2-Thio-5-thiazolidone.*

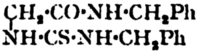
By A. H. Cook and A. L. Levy.

2-Thio-5-thiazolidone (I) reacts vigorously with primary and secondary bases to give salts of the corresponding *N*-dithiocarboxyglycine amides (*e.g.*, II). In the presence of aqueous acids these are recyclised to (I), but with anhydrous acids afford carbon disulphide and the corresponding glycine amide salts. Triethylamine or aqueous alkali causes dimerisation of (I) to a derivative of diaminoacetone, whereas pyridine and alcohols effect polymerisation to polyglycines of low molecular weight.

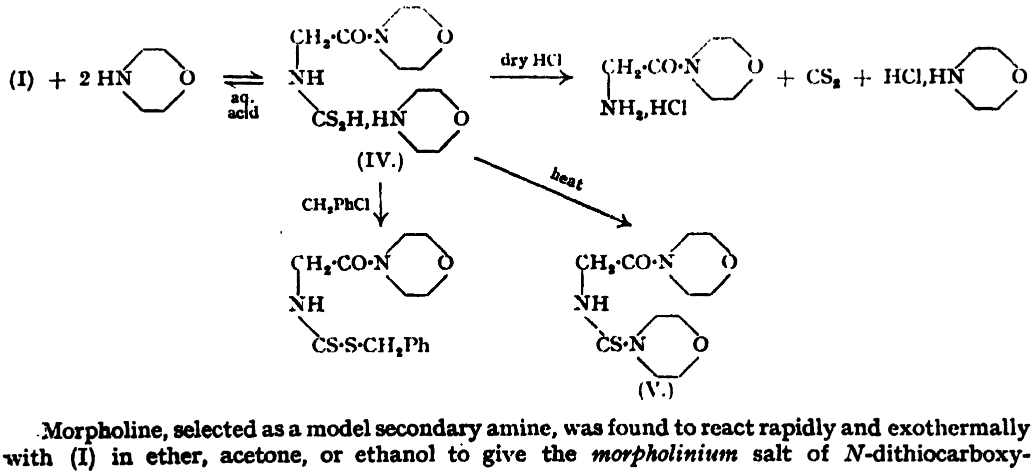
In Part III (Cook, Heilbron, and Levy, *J.*, 1948, 201) a synthesis of the novel 2-thio-5-thiazolidone (I) by the action of acids on salts of carbamylmethyldithiocarbamic acid was described. The present communication is concerned with a study of the action of bases on this compound (I).


(I.)


$$\begin{array}{l}CH_2\cdot CO\cdot NH\cdot CH_2Ph\\ NH\cdot CS_2H,NH_2\cdot CH_2Ph\end{array}$$
(II.)

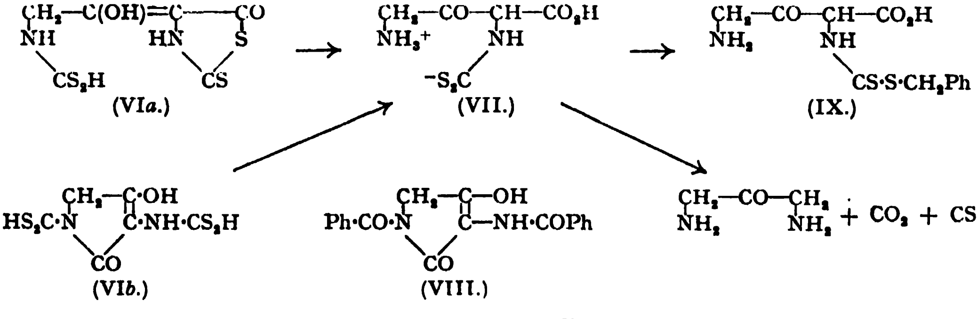

$$\begin{array}{l}CH_2\cdot CO\cdot NH\cdot CH_2Ph\\ NH\cdot CS\cdot NH\cdot CH_2Ph\end{array}$$
(III.)

When (I) was treated with benzylamine in ether at 0°, the product rapidly separated as a gum, which was presumably benzylammonium *N*-(*N'*-benzylcarbamylmethyl)dithiocarbamate (II), since it readily regenerated (I) on acidification. Dissolved in benzylamine, however, and gently warmed, (I) yielded the crystalline thiourea (III), identical with that described earlier (Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1058). It will be recalled (Cook, Harris, Heilbron, and Shaw, *loc. cit.*) that relatively minor changes in the experimental conditions gave either (III) or benzyl *N*-(*N'*-benzylcarbamidomethyl)dithiocarbamate, when 2-benzylthio-5-thiazolinone was treated with benzylamine.



Morpholine, selected as a model secondary amine, was found to react rapidly and exothermally with (I) in ether, acetone, or ethanol to give the *morpholinium* salt of *N*-dithiocarboxyglycine morpholide (IV) in a yield of 87%. This structure was confirmed by shaking (IV) with benzyl chloride in ether–water, whereupon the S-*benzyl* ester was produced. Under more vigorous conditions, however, or when (IV) was heated in methanol, hydrogen sulphide was lost and the substituted *thiourea* (V) was produced. (IV) was reconverted into (I) in 84% yield by dissolution in water and acidification with hydrochloric acid, so that the synthesis of the thiothiazolidone is by no means confined to simple carbamylalkyldithiocarbamates. Indeed, the morpholide (IV) appeared to undergo cyclisation even more readily than the simple amide. When (IV) was treated with dry hydrogen chloride in chloroform, however, another reaction took place, carbon disulphide, morpholine hydrochloride, and *glycine morpholide hydrochloride* being produced. When 3-acetyl-2-thio-5-thiazolidone (Cook, Heilbron, and Levy, *loc. cit.*) (the location of the acetyl group in the 3-position is not proven though it is supported by the low melting point of the compound) was treated with morpholine in acetone, (IV) was once again produced; the acetyl group was also detached by rapid treatment with warm concentrated hydrochloric acid, (I) being isolated.

When 2-thio-5-thiazolidone (I) was treated with triethylamine in acetone, a crystalline *salt* rapidly separated which seemed from its composition to be the triethylamine salt of (I). On acidification in water, however, it gave a labile yellow isomeride of (I), which for reasons which will now be developed is regarded as a *dimeride*, $C_6H_6O_2N_2S_4$ (VI). This substance was soluble in sodium hydrogen carbonate and gave a dark green colour with ferric chloride. The same compound was produced, to the extent of about 60%, by keeping (I) overnight in sodium hydroxide or carbonate solution, and acidifying the solution; the remaining 40% was converted into sodium carboxymethyldithiocarbamate, which decomposed to give glycine and carbon disulphide on acidification. The dimeride was freely soluble in cold acetone, methanol, or ethanol, but after a few minutes these solutions deposited colourless needles of a compound, $C_5H_8O_3N_2S_2$ (VII), which was soluble in sodium hydroxide though no longer soluble in sodium hydrogen carbonate, and gave a deep green colour, rapidly becoming purple, with ferric chloride. It afforded a reddish-purple colour with the ninhydrin reagent, was insoluble in common solvents, and melted with decomposition about 200°. Inspection of the empirical formula shows that loss of carbon disulphide and addition of the elements of water had occurred in this reaction. The compound (VII) was most conveniently prepared by dissolving the triethylamine salt of (VI) in acetic acid, whereupon it separated almost immediately in 75% yield. An important clue to the nature of these compounds was provided by acid hydrolysis of (VII), which very readily gave carbon disulphide, carbon dioxide, and 1 : 3-diaminoacetone (isolated as its *dipicrate*). The dimeride (VI) also yielded these products when boiled for a short while with 2N-hydrochloric acid, but a sulphur-containing *substance* isomeric with (VII), but of unknown structure, was formed in addition. The last-mentioned substance gave no diaminoacetone on further hydrolysis, and therefore represents an alternative path of decomposition.

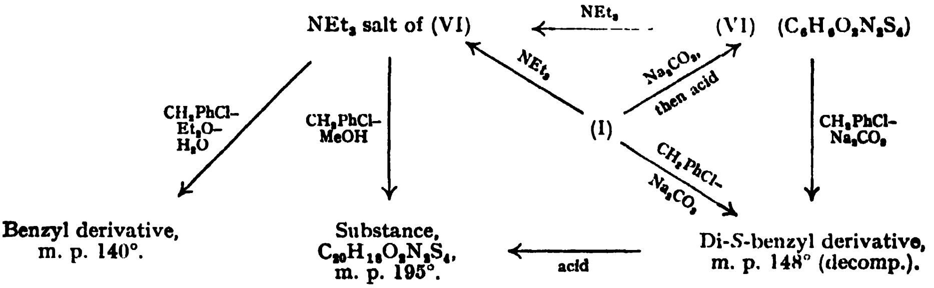


(VI*a*.) (VII.) (IX.)

(VI*b*.) (VIII.)

The isolation of diaminoacetone showed that the dimerisation reaction essentially involved attaching the carbonyl grouping of one thiazolone molecule to the active methylene group of another, yielding ultimately a ketone. Thus the simplest expression for the dimeride is the dithiocarbamic acid (VI*a*), which also satisfactorily accommodates all the known facts. Compound (VII) then becomes *γ-amino-α-dithiocarboxyaminoacetoacetic acid betaine*, the structure of which is in keeping with its zwitterionic character and ease of hydrolysis. The dimerisation of (I) recalls a similar change which takes place when 2-phenyloxazolone is treated with Grignard reagents or a mixture of triethylamine and hydrogen cyanide (Cook, Elvidge, Heilbron, and Levy, "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 738; Bailey, Baker, and Bradley, *ibid.*). The dimeride in this case has been shown to be "dibenzamidodioxytetrol" (VIII) (Cornforth and Huang, *J.*, 1948, 1958), and so the formally similar expression (VI*b*) should be considered for the dimeride of 2-thio-5-thiazolidone. This alternative expression would not seem to account so well, however, for the addition of water under mild conditions to give (VII).

When (VII) was shaken with benzyl chloride and sodium carbonate solution a mono-*S*-benzyl derivative was obtained, which formed a highly crystalline ***hydrochloride***. It was soluble in aqueous sodium hydroxide (though not in aqueous sodium carbonate) and gave an intense colour with the ninhydrin reagent, even in the presence of cupric carbonate, and is therefore formulated as the γ-amino-acid (IX). Under other conditions (I), (VI), and the triethylamine salt of (VI) give altogether three further benzyl ***derivatives***; the analyses, solubilities in alkali, and colour reactions do not, however, provide sufficient evidence on which to assign structures to them, but their interrelations are summarised in the following scheme :


NEt$_3$ salt of (VI)
NEt$_3$
(VI) ($C_6H_6O_2N_2S_4$)
NEt$_3$
Na$_2$CO$_3$, then acid
CH$_2$PhCl–Et$_2$O–H$_2$O
CH$_2$PhCl–MeOH
(I)
CH$_2$PhCl–Na$_2$CO$_3$
CH$_2$PhCl–Na$_2$CO$_3$
Benzyl derivative, m. p. 140°.
Substance, $C_{20}H_{18}O_2N_2S_4$, m. p. 195°.
acid
Di-*S*-benzyl derivative, m. p. 148° (decomp.).

Acetylation of (I), (VI), and (VII) in the presence of bases leads to a variety of derivatives dependent on quite small changes in the experimental conditions. The products contain either 2 or 3 acetyl groups, and have all to some extent lost the elements of water. While it is yet too soon to assign individual structures, it is probable from the fact that they do not give ferric chloride colours and do not regenerate the starting materials on hydrolysis, that the products are acetylated thiazoles and oxazoles formed by cyclisation of $-NH\cdot CS_2H$ and $-NH\cdot CO\cdot CH_3$ on to the enolic hydroxyl group of (VI) and (VII). The results are summarised in the table.

		Derivative of (VI) produced.		
Starting material.	Reagent.	No. of Ac groups.	Elements lost.	M. p.
(I)	Ac_2O-NEt_3	3	H_2O	137°
(VI) [a]	Ac_2O + trace of NEt_3			
"	$Ac_2O-C_5H_5N$	—	—	95
"	Ac_2O-NEt_3	2	CS_2, H_2O	158
NEt_3 derivative [b] of (VI)	Ac_2O			
NEt_3 derivative [c] of (VII)	Ac_2O-NEt_3	3	$2H_2O$	147
" " "	$Ac_2O-C_5H_5N$	—	—	173

[a] From (I) by aqueous alkali. [b] From (I) by NEt_3. [c] From (VI) by pyridine or from the NEt_3 derivative of (VI) by AcOH.

Finally, by the action of pyridine on (I), slowly in the cold or rapidly on heating, a ***substance*** was produced which was insoluble in water and all organic solvents, and soluble only in concentrated hydrochloric acid and aqueous alkalis. Since most of the sulphur had been lost, the material is regarded as a crude polyglycine. It is worth recalling that pyridine rapidly effects the expulsion of carbon dioxide from the analogous anhydrocarboxyamino-acids, with accompanying polymerisation (*inter alia*, Wesseley and Sigmund, *Z. physiol. Chem.*, 1926, 157, 91). A Van Slyke amino-nitrogen determination indicated a molecular weight of 605 per terminal $-NH_2$, which corresponds to about 9 glycine residues, in fair agreement with the analytical figures, which indicate one atom of sulphur in such a molecule. Insoluble high-melting substances of similar gross composition were also produced by refluxing (I) for a short time in methanol or ethanol, the methoxyl content of a product from the former solvent indicating an average molecular length of 8 glycine residues.

EXPERIMENTAL.

Action of Benzylamine on (I).—2-Thio-5-thiazolidone (1·0 g.) was dissolved in dry ether, and benzylamine (1·61 g., 2 equivs.) added at 0°. A white solid separated at once, which became gummy on exposure to air and afforded (I) on acidification with 2N-hydrochloric acid.

Action of Morpholine on (I).—Morpholine (1·8 g., 2 equivs.) was added to 2-thio-5-thiazolidone (1·3 g.) in acetone (20 c.c.) at 0° during 2 minutes, and the product (2·6 g., 87%), m. p. 127° (decomp.), filtered off after 15 minutes at room temperature. The *morpholinium* salt of *N*-dithiocarboxyglycine-morpholide (IV) recrystallised from aqueous acetone in rectangular prisms, m. p. 142° (decomp.) (Found: C, 43·4; H, 6·4; N, 13·6. $C_{11}H_{21}O_3N_3S_2$ requires C, 43·0; H, 6·8; N, 13·7%), though after crystallisation from hot methanol the m. p. rose to 193°, giving (V). It gave a colourless precipitate with aqueous mercuric chloride, a creamy precipitate (decomp. 100°) with lead acetate, and a pale yellow silver salt which rapidly darkened and was black after 1—2 minutes. The salt (IV) was shaken with excess of benzyl chloride in ether–water for 2·5 hours, whereupon the *benzyl* ester separated; it recrystallised from ethanol in star-like clusters of needles, m. p. 135—136° (Found: C, 54·2; H, 6·1; N, 8·8. $C_{14}H_{18}O_2N_2S_2$ requires C, 54·2; H, 5·8; N, 9·0%). (I) (1·3 g.) was warmed on the steam-bath with morpholine (10 c.c.) for 5 minutes and diluted with acetone to give the substituted *thiourea* (V) (0·7 g.), m. p. 195—196° (decomp.) (after crystallisation from methanol or water) (Found: N, 15·5. $C_{11}H_{19}O_3N_3S$ requires N, 15·4%).

The salt (IV) (2·6 g.) in water (10 c.c.) was treated with concentrated hydrochloric acid (3 c.c.) at 0°, whereupon (I) (0·95 g., 84%) separated immediately. When dissolved in chloroform, however, and treated with dry hydrogen chloride, (IV) gave *glycine morpholide hydrochloride*, m. p. 238°, after evaporation and crystallisation of the residue from ethanol (Found: C, 40·8; H, 7·2; N, 14·9. $C_6H_{13}O_2N_2Cl$ requires C, 39·9; H, 7·2; N, 15·5%). Addition of ether to the filtrate gave morpholine hydrochloride, m. p. 178—179° (after recrystallisation from methanol–ether).

3-Acetyl-2-thio-5-thiazolidone (Cook, Heilbron, and Levy, *loc. cit.*) with morpholine in acetone or ethyl acetate afforded (IV), m. p. 137° (decomp.), when seeded and scratched. When the acetyl derivative was warmed with concentrated hydrochloric acid until dissolved, (I) separated in flakes on cooling, and was identified by its ability to give an intense purple colour with iodine in the presence of sodium acetate and by the characteristic formation of long needles on recrystallisation from benzene.

The Dimerisation of (I).—2-Thio-5-thiazolidone (1·3 g.) in acetone (15 c.c.) was treated with triethylamine (1·0 g., 1 equiv.) under nitrogen, and the resulting *bistriethylamine* salt (1·4 g., 61%), m. p. 133° (decomp.), collected after 20 minutes, washed with acetone to remove a little colour, and analysed directly (Found: C, 46·55; H, 7·9; N, 11·9. $C_6H_6O_2N_2S_4,2C_6H_{15}N$ requires C, 46·1; H, 7·7; N, 11·9%). The yield was not improved by using 2 equivalents of triethylamine. It was soluble in water, methanol, chloroform, or pyridine, insoluble in ethanol, ether, or ethyl acetate, and was best recrystallised from methanol–ethyl acetate. The triethylamine salt was unstable, changing to a black tar when kept overnight, and solutions rapidly developed intense red and purple colours on exposure to air. Treatment with morpholine in chloroform caused separation of the corresponding morpholine salt, m. p. 154° (decomp.).

When the triethylamine salt was dissolved in water and acidified with concentrated hydrochloric acid at 0°, a yellow gum was precipitated which solidified after a little scratching to give the dimeride (see below). Conversely, the triethylamine or morpholine salt was obtained, when this was treated with the appropriate base in acetone. The *dimeride* (VI) (4·5 g., 64%) was best prepared by keeping (I) (7·0 g.) in 10% sodium hydroxide solution (40 c.c.) overnight under nitrogen and then acidifying the solution at 0° (Found: C, 27·4; H, 2·4; S, 47·7. $C_6H_6O_2N_2S_4$ requires C, 27·1; H, 2·3; S, 48·1%); carbon disulphide was present in the filtrate. The same results were obtained using sodium carbonate solution. Thus secured, the dimeride darkened gradually at >200°, obvious decomposition setting in at >250°. It was soluble in aqueous sodium hydrogen carbonate with effervescence, the solution darkening if exposed to air, and was precipitated unchanged on acidification. It was insoluble in benzene, ethyl acetate, ether, or chloroform, but freely soluble in cold acetone or methanol, and rather less so in ethanol.

When kept for 5—10 minutes, or immediately when boiled or treated with pyridine, the above solutions deposited the *betaine* (VII) which decomposed indefinitely above 200°, was insoluble in all common solvents, and could be recrystallised from a large volume of water in long, colourless needles (Found: C, 29·3; H, 4·2; N, 13·0; S, 30·6. $C_5H_8O_3N_2S_2$ requires C, 28·9; H, 3·9; N, 13·5; S, 30·8%). The compound was soluble in aqueous sodium hydroxide, whence it was reprecipitated by acids, difficultly soluble in sodium carbonate, and insoluble in sodium hydrogen carbonate. The compound was most conveniently prepared by dissolving the triethylamine salt of (VI) (4·2 g.) in acetic acid (25 c.c.) under nitrogen, and collecting the crystals (1·4 g., 75%) after 0·5 hour.

Acid Hydrolyses.—The above compound (VII) (0·5 g.) was heated under reflux with 2N-hydrochloric acid (10 c.c.) for 3 minutes, by which time a clear solution had resulted. Carbon disulphide was observed as oily drops in the condenser, and carbon dioxide was detected with saturated aqueous barium hydroxide in the usual way. Evaporation gave diaminoacetone dihydrochloride which was not readily purified but with picric acid yielded 1 : 3-*diaminoacetone dipicrate* which crystallised from dilute aqueous picric acid in long yellow needles, m. p. 210—215° (decomp.) (Found: C, 31·9; H, 3·0. $C_3H_8ON_2,2C_6H_3O_7N_3,H_2O$ requires C, 31·9; H, 2·9%). The same dipicrate was prepared from authentic diaminoacetone, obtained by hydrolysis of "dibenzamidodioxytetrol" (Rügheimer, *Ber.*, 1888, **21**, 3325). The betaine (VII) was also decomposed by boiling it with water for 15 minutes, but addition of picric acid failed to yield the above picrate in this case.

The dimeride (VI) (1·5 g.) was heated under reflux with 2N-hydrochloric acid (10 c.c.) for 10 minutes, dissolving with vigorous effervescence (carbon dioxide) and production of carbon disulphide. The solution was evaporated, and the yellow gum dissolved in water (8 c.c.), granular prisms (0·5 g.), m. p. 177° (decomp.), being slowly deposited; the filtrate gave diaminoacetone dipicrate (0·25 g.) with picric acid. The above *substance* was recrystallised from water containing a little hydrochloric acid, whence it separated slowly and had m. p. 174° (decomp.) (Found: C, 29·3, 28·6; H, 4·3, 3·7; N, 14·6, 12·5. $C_5H_8O_3N_2S_2$ requires C, 28·9; H, 3·9; N, 13·5%). It was sparingly souble in common solvents, soluble in aqueous sodium hydroxide though not in sodium hydrogen carbonate and was recovered unchanged after being heated for 0·5 hour at 100° with 2N-hydrochloric acid. The dimeride (VI) was transformed in poor yield into (VII) when boiled with water.

Benzylation Experiments.—Compound (VII) (0·77 g.) was suspended in 2N-sodium carbonate (10 c.c.)

and shaken overnight with benzyl chloride (2 c.c.) and ether (10 c.c.). The insoluble benzyl derivative (0·64 g.), m. p. 180° (decomp.), was recrystallised from 2N-hydrochloric acid as its *hydrochloride*, in colourless needles, m. p. 194—195° (decomp.) (Found: C, 43·8; H, 4·4; N, 8·3; Cl, 11·0. $C_{12}H_{14}O_3N_2S_2$,HCl requires C, 43·1; H, 4·5; N, 8·4; Cl, 10·6%). It was soluble in methanol and insoluble in acetone, and gave a green colour with ferric chloride in methanol. If insufficient acid was present during the recrystallisation, the free base, m. p. 178° (decomp.), separated, insoluble in methanol and hot water, though soluble in hot sodium carbonate solution and cold sodium hydroxide solution. The amino-acid, when heated with ninhydrin and sodium acetate, gave a reddish colour becoming intense green in the presence of cupric carbonate. DL-Alanine gave no colour under these conditions.

2-Thio-5-thiazolidone (I) (5·0 g.) in 2N-sodium carbonate (50 c.c.) was shaken overnight with benzyl chloride (5 c.c.) in ether (30 c.c.) under nitrogen; an insoluble *S*-benzyl derivative (4·0 g.), m. p. 148° (decomp.), was produced. Acidification of the aqueous layer gave *N*-dithiocarbobenzyloxyglycine (1·2 g.), m. p. 164°. The benzyl derivative was soluble in acetone and ethyl acetate, sparingly soluble in cold methanol or ethanol, and insoluble in ether, chloroform, or light petroleum; it decomposed in hot solvents. The same compound (1·2 g.) was produced when (VI) (1·0 g.) in 2N-sodium carbonate (20 c.c.) was shaken with benzyl chloride (1·5 c.c.) in ether for 1·5 hours under nitrogen. In acetone, it gave a deep indigo-blue colour with ferric chloride, extractable into chloroform, which became green with excess of ferric chloride.

When the preceding benzyl derivative was crystallised rapidly from hot acetic acid, a *compound* separated in needles, m. p. 195° (decomp.) (Found: C, 53·9; H, 4·2; N, 6·5; S, 28·3. $C_{20}H_{18}O_2N_2S_4$ requires C, 53·8; H, 4·0; N, 6·3; S, 28·7%). The acidity of the acetic acid was responsible for this change, which was more conveniently effected by adding a few drops of concentrated hydrochloric acid to an acetone solution of the lower-melting benzyl derivative, whereupon the compound, m. p. 195°, was quantitatively precipitated. It was insoluble in common solvents, and gave a deep green colour when warmed with methanolic ferric chloride. Both benzyl derivatives were insoluble in cold 2N-sodium hydroxide, but dissolved on heating, with liberation of toluene-ω-thiol; acidification gave a yellow flocculent precipitate. When the triethylamine salt of (VI) was warmed with benzyl chloride in methanol or chloroform, the benzyl derivative, m. p. 195° (decomp.), rapidly separated. When shaken overnight with benzyl chloride (3 c.c.) in ether (10 c.c.) and water (8 c.c.), however, the triethylamine salt (2·6 g.) yielded a different benzyl derivative (1·9 g.), m. p. 140° (decomp.). This was unaffected by cold dilute acids, but was soluble in cold 2N-sodium hydroxide liberating triethylamine, whereafter acidification afforded a yellow precipitate, m. p. 110° (decomp.) after contracting at 76°.

Acetylation Experiments.—The bistriethylamine salt of (VI) was warmed with excess of acetic anhydride for a few minutes, cooled, scratched, and diluted with water to give a *diacetyl* derivative, m. p. 157—158°, colourless needles from ethanol (Found: C, 40·5; H, 2·9; N, 10·7; S, 25·5. $C_9H_8O_3N_2S_2$ requires C, 42·2; H, 3·1; N, 10·9; S, 25·0%). The compound was insoluble in cold 2N-sodium hydroxide, dissolving on heating to give a yellow-orange solution, and did not give an insoluble picrate or hydrochloride in benzene. (VI) itself was not acetylated smoothly, though when an equivalent quantity of triethylamine was present, the above acetyl derivative was obtained. With only a trace of triethylamine, however, an acetyl derivative, m. p. 137°, was secured, which appeared to be the same as that obtained from (I) and acetic anhydride–triethylamine (see below). When (VI) was covered with acetic anhydride and a drop of pyridine added, immediate reaction led to the separation of a colourless crystalline mass, m. p. 95° (vigorous decomp.) (after being washed with ethanol). This was clearly of a different character from the other acetyl derivatives mentioned in this section. (VII) dissolved in hot acetic anhydride–pyridine to give an orange solution; dilution with water and crystallisation of the product from aqueous ethanol then gave colourless needles, m. p. 173° (slight decomp.). When (VII) was boiled for a few moments with acetic anhydride–triethylamine, cooled, and diluted with ethanol, a *triacetyl* derivative was obtained which crystallised from ethanol in rosettes of small needles, m. p. 147° (Found: C. 44·8; H, 3·6; N, 9·9; S, 21·7. $C_{11}H_{10}O_4N_2S_2$ requires C, 44·3; H, 3·4; N, 9·4; S, 21·5%). The compound did not yield a picrate in benzene, and was deacetylated with warm 2N-hydrochloric acid to give a product, m. p. 165° (decomp.). 2-Thio-5-thiazolidone (I) was suspended in acetic anhydride; addition of triethylamine caused an exothermic reaction and development of a red colour. After 2 hours, the *triacetyl* derivative was collected and recrystallised from chloroform–ethanol, having m. p. 135—137° (Found: C, 38·6; H, 2·8; N, 8·1; S, 34·3. $C_{12}H_{10}O_4N_2S_4$ requires C, 38·5; H, 2·7; N, 7·5; S, 34·2%). Attempts to recrystallise the material from dilute acetic acid or ethanol led to deacetylation, and the production of a compound, m. p. 198° (decomp.), which was reconverted into the original triacetyl derivative by acetic anhydride–triethylamine. The triacetyl derivative was insoluble in cold 2N-sodium hydroxide, but dissolved on warming.

Polymerisation of (I).—2-Thio-5-thiazolidone (1·0 g.) was kept in the dark in pyridine (10 c.c.) for 18 hours under nitrogen, and the yellow solid (0·45 g.) which had separated, was washed well with pyridine and then with acetone (Found, after drying for 4 hours at 100°/0·1 mm.: C, 38·5; H, 5·1; N, 14·4; S, 6·4%). The substance decomposed indefinitely above 200°, and was insoluble in common solvents, including hot pyridine and acetic acid. It was almost wholly soluble in aqueous sodium hydrogen carbonate, carbonate, or hydroxide, but only a small recovery was obtained on acidification of such solutions. It was soluble in concentrated hydrochloric acid and in hot dilute acid, though almost insoluble in hot water. In another experiment, (I) (0·2 g.) was boiled with pyridine (5 c.c.) for 2—3 minutes under nitrogen, and the polymer filtered off, washed well with pyridine, and dried for 4 hours at 100°/0·1 mm. [Found: C, 38·4; H, 5·5; N, 19·5; S, 5·5; amino-N (Van Slyke; kindly determined by Dr. J. L. Bailey), 2·3%].

2-Thio-5-thiazolidone (0·5 g.) was heated under reflux with methanol (10 c.c.) for a few minutes in nitrogen, and the colourless granular product filtered off and well washed with hot methanol {Found (in 2 different samples, both dried for 3 hours at 80°/0·1 mm.): C, 37·7, 38·7; H, 5·4, 5·5; N, 19·7, 20·0; S, 7·75, 7·6; MeO, 5·8. $C_{18}H_{28}O_9N_8S_2$ (*i.e.*, $HS_2C{\cdot}[NH{\cdot}CH_2{\cdot}CO]_8{\cdot}OMe$) requires C, 38·4; H, 5·0; N, 19·9; S, 11·3; MeO, 5·7%}. Similar results were obtained by using ethanol, though precipitation was slower. The products were soluble in concentrated hydrochloric acid, and in sodium hydroxide on warming, but could not be suitably recovered by dilution with water or acidification, respectively. They were insoluble in hot pyridine or acetic acid, but readily soluble in formic acid.

We express our gratitude to Sir Ian Heilbron, D.S.O., F.R.S., for his interest, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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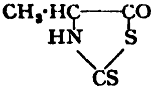
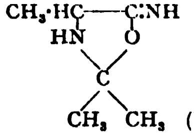
124. *Studies in the Azole Series. Part XXVI. The Action of Bases on 2-Thio-4-methyl-5-thiazolidone.*

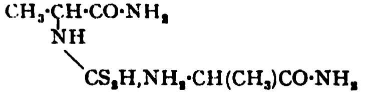
By A. H. COOK and A. L. LEVY.

2-Thio-4-methyl-5-thiazolidone (I) exhibits a markedly greater stability than its analogue discussed in the preceding paper. While the ring is still readily opened by ammonia and morpholine, the products tend to revert in large part to (I) on acidification, even under anhydrous conditions. The carbon disulphide can be liberated from the ammonium dithiocarbamate, however, by very slow acidification in water under controlled conditions. (I) polymerises in boiling pyridine, but is stable to cold triethylamine.

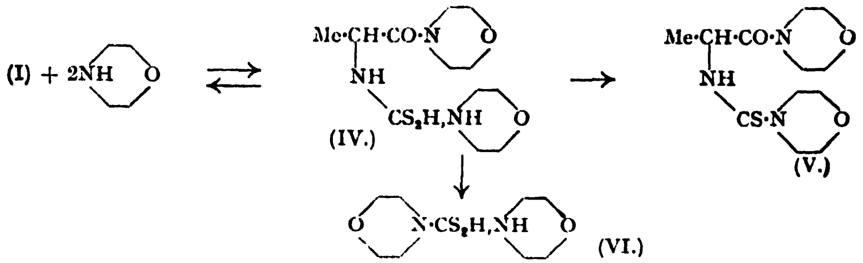
IN view of the reactivity of 2-thio-5-thiazolidone and as a model for 4-substituted thiothiazolidones, (±)-2-thio-4-methyl-5-thiazolidone (I) was selected for study. The preparation of α-aminopropionitrile was improved, and the base condensed with acetone in the presence of sodium methoxide (cf. Cook, Heilbron, and Levy, Part III, *J.*, 1948, 201) to give 5-imino-2 : 2 : 4-trimethyloxazolidine (II). With carbon disulphide in wet acetone, this afforded *α-carbamylethylammonium α-carbamylethyldithiocarbamate* (III), which yielded the required *thiothiazolidone* (I) in 90% yield on acidification with two equivalents of 2N-sulphuric acid. Acidification with dry hydrogen chloride in ethanol gave alanine amide hydrochloride in 60% yield, also obtained from (II) and hydrochloric acid. While α-aminopropionitrile was available, advantage was taken of the experience gained with aminoacetonitrile, to improve its condensation with carbon disulphide (Cook, Heilbron, and Levy, *J.*, 1947, 1598), and *4-amino-2-mercapto-4-methylthiazole* was obtained directly in 61% yield. It readily formed a Schiff's *base* with pyruvic acid, but could not be converted into (I) with acids.


(I.)


(II.)


(III.)

When (I) was treated with ammonia in ethanol, 90% of *ammonium α-carbamylethyldithiocarbamate* (cf. III) rapidly crystallised. On acidifying a solution of the ammonium salt in water, (I) was recovered in high yield, but treatment with dry hydrogen chloride in ethanol gave crude alanine amide hydrochloride in 64% yield, only 12% undergoing ring-closure to (I). Alternatively, methanolic picric acid could be used to provide crude alanine amide picrate in 70% yield, ammonium picrate being recovered quantitatively. It was of interest to see, using ammonium α-carbamylethyldithiocarbamate as a model, whether carbon disulphide could also be detached by a more controlled acidification in water. It was therefore slowly titrated against 0·05N-hydrochloric acid, the changes in pH being followed with a glass electrode. The initial pH (6·26) fell on addition of acid as the dithiocarbamic acid corresponding to (III) was liberated. Thereafter the pH began to rise, following a unimolecular curve and becoming constant after about five minutes. Clearly, this stage corresponded to loss of carbon disulphide from α-carbamylethyldithiocarbamic acid to give alanine amide, which would however be expected to neutralise at once any undecomposed acid to give (III), resulting in only half the theoretical quantity of carbon disulphide being lost for each addition of acid. This was borne out by the final titration curve which showed that two equivalents of acid were required to expel all the carbon disulphide. The course was constructed by observing the pH of the solution at an arbitrarily standardised time of three minutes after the addition of each drop of acid, *i.e.*, when about 85% of the α-carbamylethyldithiocarbamic acid had decomposed. Carbon disulphide separated from the solution during the titration, which took several hours, and no thiothiazolidone (I) was produced. For comparison, ammonium α-carbamylethyldithiocarbamate was titrated against 0·1N-hydrochloric acid during 11 minutes; in this case (I) separated from the solution, and the curve obtained was quite different from that obtained by slow titration, the first half being of the expected form for neutralisation of an ammonium salt. It appeared, therefore, that very slow acidification allowed α-carbamylethyldithiocarbamic acid to decompose before the pH became sufficiently low to cause thiothiazolidone formation. In order to gain some estimate of this pH value, the ammonium salt was acidified with a series of buffer solutions (pH 1·26—2·8). Crystallisation of (I) practically ceased at pH 2·5, though by working with a very concentrated solution a small degree of cyclisation was brought about by potassium hydrogen phthalate (pH 4). Hence, ring-closure of (III) and the corresponding ammonium salt to (I) was readily effected by such compounds as aqueous oxalic, sulphurous, and acetic acids, an 85% yield being obtained with acetic acid.


(IV.)

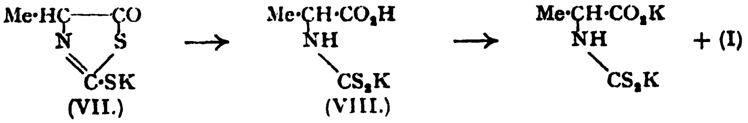
(V.)

(VI.)

When (I) was kept with two equivalent proportions of morpholine in acetone solution, the crystalline *morpholinium* salt of *N*-dithiocarboxyalanine morpholide (IV) soon separated in a yield of 89%. Acidification of this salt regenerated (I) in a yield of 87%. The salt was remarkably labile, for when kept for a short time in solvents it was completely decomposed to a mixture of the substituted *thiourea* (V) and the morpholinium salt of 4-dithiocarboxymorpholine (VI), each of which could be isolated under appropriate conditions. When (I) was warmed with excess of morpholine, (VI) was the main product, treatment of which with aqueous acid gave the corresponding unstable free dithiocarbamic acid. Acidification of (IV) with dry hydrogen chloride in chloroform gave a poor yield of crude alanine morpholide hydrochloride, and 44% of the dithiocarbamate reverted to (I). This contrasts with the ready expulsion of carbon disulphide from the corresponding glycine derivative (preceding paper), and indicates the considerable influence of the methyl substituent in promoting ring-closure.

Again unlike 2-thio-5-thiazolidone, (I) was unaffected by triethylamine in cold acetone, and did not yield an insoluble polymer when heated under reflux with methanol However, in boiling pyridine, a high-melting, insoluble compound was produced after some time, which is probably a lower polyalanine.

The thiothiazolidone (I) dissolved in one equivalent of aqueous barium hydroxide or potassium hydroxide to give a solution of pH 8·5, which slowly became more acid on storage. When the pH had reached 7·7 (after 11 minutes) colourless needles began to separate, which increased in amount during several hours. Surprisingly, these were identified as (I), and its formation was evidently due to slow ring-opening of (VII) to give the carboxylic acid (VIII), which being a comparatively strong acid captured the limited number of potassium ions present from the weakest acid, namely (I). The salt (VII) was also decomposed by carbon dioxide to give (I).


(VII.)

(VIII.)

At pH 9, approximately one-third of (I) decomposed during the first hour, and no evidence was obtained of dimerisation under the influence of alkali, as was the case with 2-thio-5-thiazolidone.

EXPERIMENTAL.

2-Thio-4-methyl-5-thiazolidone and Related Compounds.—In our hands, the following preparation of α-aminopropionitrile gave better results than that described in Part II (*J.*, 1947, 1598), and by Goldberg and Kelly (*J.*, 1947, 1371). Acetaldehyde (180 g.; freshly prepared from paraldehyde) and hydrogen cyanide (160 c.c.) were mixed in a large flask cooled in a freezing mixture, 50% aqueous potassium hydroxide cautiously added to initiate the vigorous autocatalytic reaction, and addition subsequently continued until no further heating effect was produced (2—3 c.c. required). After 1 hour at room temperature, the catalyst was neutralised with concentrated sulphuric acid, and the mixture filtered and distilled at 10—12 mm. After an initial fraction, b. p. ~50° (paraldehyde), acetaldehyde cyanohydrin (105 g., 36%) distilled smoothly at 92°. Commercial acetaldehyde gave variable results by this procedure, though one batch (600 g.) gave a 60% yield of cyanohydrin. The cyanohydrin (167 g.) was added to a solution of liquid ammonia (100 g.) in methanol (500 c.c.), and the mixture kept at room temperature for 22·5 hours. Excess of methanol and ammonia was removed in a vacuum, and the residue distilled at 10—12 mm., an initial fraction (mainly water) being followed by the pure α-aminopropionitrile (78·5 g., 48%), b. p. 64°.

α-Aminopropionitrile (10 g.) in dry acetone (20 c.c.) was treated with a solution of sodium (~0·2 g.) in dry ethanol (~2 c.c.), the mixture becoming slightly warm. Next morning, the mixture was cooled in a freezing mixture and scratched, whereupon 5-imino-2 : 2 : 4-trimethyloxazolidine (9·2 g., 50%) separated, having m. p. 76°. Like the glycine analogue, it was deliquescent, but solidified again owing to carbonate or carbamate formation. With concentrated hydrochloric in ethanol, it yielded alanine amide hydrochloride, m. p. 172—173°. When the above acetone filtrate was treated with carbon disulphide, it yielded *α-carbamylethylammonium α-carbamylethyldithiocarbamate* (III) (4·0 g.), which crystallised from water on addition of a large excess of acetone, in rectangular tablets, m. p. 140° (decomp.) (varies with the rate of heating) (Found : C, 33·35; H, 6·6; N, 22·5. $C_7H_{16}O_2N_4S_2$ requires C, 33·35; H, 6·4; N, 22·2%).

When (III) was dissolved in water, and acidified, the required *2-thio-4-methyl-5-thiazolidone* rapidly separated in high yield, and recrystallised from benzene in beautiful blades, m. p. 128·5° (Found : C, 33·0; H, 3·8; N, 9·3. $C_4H_5ONS_2$ requires C, 32·65; H, 3·4; N, 9·5%). The thiothiazolidone was freely soluble in methanol, ethanol, acetone, ethyl acetate, or ether, moderately in chloroform or acetic acid, and insoluble in water or light petroleum. It dissolved readily in aqueous sodium hydroxide or carbonate, but was insoluble in sodium hydrogen carbonate. After treatment with hydroxylamine hydrochloride and sodium acetate in methanol, it afforded an intense brown colour (and a precipitate in stronger solutions) with ferric chloride. 2-Thio-5-thiazolidone gave the same colour (though the iodine–sodium acetate test is more characteristic in this case; cf. Part III, *J.*, 1948, 204), as do many other 4-substituted-5-thiazolidones and anhydrides generally (Davis and Levy, *J.*, in the press).

For the preparation of 2-thio-4-methyl-5-thiazolidone (I) in the best yield, it was not necessary to isolate α-aminopropionitrile or the above iminotrimethyloxazolidine, and a typical procedure was as follows. Acetaldehyde cyanohydrin (80 g.) was added to a mixture of liquid ammonia (40 c.c.) and methanol (40 c.c.) cooled initially in ice, and kept for 24 hours at room temperature. Excess of methanol and ammonia was then evaporated off on a water pump, until the temperature of the distilling liquid had reached 55°, and the residue was dissolved in dry acetone (150 c.c.), treated with sodium ethoxide (~0·5 g.), and kept overnight. The mixture was then diluted with acetone (250 c.c.) containing water (20 c.c.) and seeded, whereafter addition of carbon disulphide (40 c.c.) with vigorous stirring and scratching caused the dithiocarbamate (III) (47·5 g., 33% calc. on the cyanohydrin) to separate. This was dissolved in water and acidified with 2N-sulphuric acid (190 c.c.). 2-Thio-4-methyl-5-thiazolidone (25 g., 90%), m. p. 125—126°, rapidly crystallised. Recrystallisation from benzene gave 18 g., m. p. 127—128°.

The dithiocarbamate (III) (1·26 g.) was suspended in dry ethanol (10 c.c.), and a stream of dry hydrogen chloride in nitrogen (made by bubbling nitrogen through concentrated hydrochloric acid, followed by passage through anhydrous calcium chloride) passed in for 2 hours. (III) dissolved, and was replaced by crude alanine amide hydrochloride (0·74 g., 60%), m. p. 165—168°.

α-Aminopropionitrile (4·5 g.) was treated with excess of carbon disulphide in ethyl acetate, whereupon *5-amino-2-mercapto-4-methylthiazole* (5·7 g., 61%) separated on scratching, and recrystallised from ethanol in pale yellow needles which contracted and resolidified at about 150°, became dark purple at 220°, and decomposed completely at 233° (Found : C, 33·4; H, 4·0. $C_4H_6N_2S_2$ requires C, 32·9; H, 4·1%). When the reaction was carried out in ethanol, the product was incompletely soluble in hot ethanol, the residue being 2 : 4-dithio-5-methylhydantoin, m. p. 223° (decomp.) (cf. Cook, Heilbron, and Levy, *loc. cit.*). When the aminothiazole was dissolved in 2N-hydrochloric acid, it was rapidly replaced by white needles of the hydrochloride, m. p. 207° (decomp.); on the mixture being warmed to 70° for 1 minute a flocculent precipitate, m. p. 195—200° (decomp.), was deposited. The aminothiazole gave a clear solution in 2N-nitric acid, which slowly deposited the above compound, m. p. 195—200° (decomp.), in poor yield on storage for some hours; (I) was not obtained. When treated with pyruvic acid in methanol, the thiazole gave an immediate orange precipitate of *5-α-carboxyethylideneamino-2-mercapto-4-methylthiazole* which crystallised from acetic acid in clusters of needles, m. p. 199° (decomp.) (Found : C, 39·2; H, 3·8. $C_7H_8O_2N_2S_2$ requires C, 38·9; H, 3·7%).

Experiments with Ammonium α-Carbamylethyldithiocarbamate.—2-Thio-4-methyl-5-thiazolidone (2·0 g.) in ethanol (25 c.c.) was treated with liquid ammonia (3 c.c.). Ammonium α-carbamylethyldithiocarbamate (2·2 g., 90%) was collected after 45 minutes, and recrystallised from methanol–ether; it then had m. p. 143°. With aqueous silver nitrate it gave a momentary white precipitate which rapidly became yellow and then black. Lead acetate gave a yellow precipitate which began to deposit a lead sulphide "mirror" after 5 minutes, whereas mercuric chloride gave a clean, almost white derivative.

The ammonium salt (1·0 g.) was suspended in dry ethanol (10 c.c.), and dry hydrogen chloride passed in with cooling until the mixture was acid to Congo-red. Ammonium chloride (0·3 g.) was filtered off, and the filtrate evaporated to dryness in a vacuum and treated with a small volume of ethanol to give crude alanine amide hydrochloride (0·25 g.), m. p. 158° (decomp.). Re-evaporation and trituration of the residue with acetone gave a second crop (0·19 g.), m. p. 154° (decomp.). The final filtrate was evaporated, and the residue treated with water to give (I) (0·08 g., 12%), m. p. 126—128°. The combined crops of amide hydrochloride (0·44 g., 64%) were recrystallised thrice from acetic acid; the colourless needles produced had m. p. 176°, undepressed with an authentic specimen.

Picric acid (1·15 g.) was dissolved in warm methanol (10 c.c.), and a suspension of the above ammonium salt (0·45 g.) in warm methanol (7 c.c.) added. The solution became clear, whereafter cooling in a freezing mixture gave ammonium picrate (0·53 g., 87%), m. p. ~250° (decomp.). The filtrate was evaporated in a vacuum, and four crops of crude alanine amide picrate (total: 0·58 g., 74%) were obtained by dissolution of the residue in acetone and precipitation with ether and light petroleum. The combined material was recrystallised from water; a small first crop was ammonium picrate, the remainder (0·27 g.; 36%) being alanine amide picrate, m. p. 192—200°, undepressed on admixture with an authentic sample (m. p. 197°).

The slow-titration experiment was performed at 22° on 3·997 mg. (0·0221 mg.-equivalent) of the ammonium salt in water (1·0 c.c.), in a micro-titration apparatus described by Catch, Cook, and Kitchener (*J.*, 1945, 319), using a standard Cambridge pH meter and glass electrode. Addition of 0·897 c.c. of 0·0497N-hydrochloric acid (*i.e.*, 0·0445 mg.-equivalent) was required to reach the end-point. In the rapid-titration experiment, 1·0 c.c. of 0·5N-ammonium α-carbamylethyldithiocarbamate was neutralised with 5·0 c.c. of 0·1N-hydrochloric acid in a Morton cell, stirring being effected with a fine stream of nitrogen.

Buffer solutions of pH 1·26, 1·88, 2·16, 2·5, and 2·8 were prepared by mixing 0·1N-glycine solution (0·1N. also with respect to sodium chloride) with 0·1N-hydrochloric acid in the following proportions: 2 : 8, 5 : 5, 6 : 4, 7 : 3, 8 : 2. 0·5N-Ammonium α-carbamylethyldithiocarbamate (1 c.c.) was added to each (10 c.c.); precipitation of (I) by the first two appeared to be as complete as with 0·05N-hydrochloric acid. A smaller quantity crystallised from the solution having pH 2·16, and hardly any from that having pH 2·5. α-Carbamylethylammonium α-carbamylethyldithiocarbamate (III) (5·0 g.) was dissolved in water and acidified with glacial acetic acid (*ca.* 3 c.c.), whereupon 2-thio-4-methyl-5-thiazolidone (2·45 g., 85%) separated slowly in well-formed plates. When the corresponding ammonium salt was acidified with aqueous picric acid, however, ammonium picrate was precipitated, and (I) was not produced.

Action of Morpholine on (I).—2-Thio-4-methyl-5-thiazolidone (1·5 g.) in acetone (25 c.c.) was treated with morpholine (1·8 g., 2 equivs.). Heat was evolved and the *morpholinium* salt (IV) (2·9 g., 89%) of *N*-dithiocarboxyalanine morpholide separated on scratching, and was recrystallised from chloroform by the addition of ethyl acetate containing a little ether, forming microprisms, m. p. 115° (decomp.; partly resolidifying to remelt at ~175°) (Found: C, 44·2; H, 7·3. $C_{12}H_{23}O_3N_3S_2$ requires C, 44·9; H, 7·2%). The reaction could also be carried out in methanol, the dithiocarbamate separating in well-formed rectangular prisms, m. p. 110° (decomp.), on seeding. If the solution was not seeded, however, the thiourea (V) (see below), m. p. 159°, crystallised on storage overnight, whereas, if the dithiocarbamate (IV) was dissolved in methanol, morpholinium dithiocarbamate (VI) (see below), m. p. 219° (sealed tube), separated on storage (especially if the solution had been warmed).

When the compound (IV) (2·9 g.) was dissolved in water (20 c.c.) and acidified with concentrated hydrochloric acid, 2-thio-4-methyl-5-thiazolidone (1·15 g., 87%), m. p. 123—125°, was immediately precipitated. (IV) (1·0 g.) in dry chloroform (20 c.c.) was saturated with dry hydrogen chloride, and evaporated to dryness in a vacuum. Treatment of the residue with ethanol and then acetone gave 3 crops of crystals (0·68 g., total), the final filtrate giving (I) (0·2 g., 44%), m. p. 124°, on dilution with water. Fractionation of the above crystals from ethanol cooled in a freezing mixture gave the less soluble morpholine hydrochloride, m. p. 175—176°, and crude alanine morpholide hydrochloride, m. p. 153—156°. The latter became damp on exposure to air, changing to a compound, m. p. 251° (decomp.), after crystallisation from ethanol.

In an attempted crystallisation of (IV) from methanol–ethyl acetate, very little of the required compound was obtained, and evaporation of the filtrate yielded the substituted *thiourea* (V), m. p. 159°, which recrystallised from benzene–light petroleum in clusters of rods, m. p. 161—162° (Found: C, 50·0; H, 7·7; N, 14·5. $C_{12}H_{21}O_3N_3S$ requires C, 50·2; H, 7·3; N, 14·6%). It could also be crystallised from water, or in diamond-shaped prisms from methanol or ethanol. When (I) was warmed with excess of morpholine for a few moments without a solvent, morpholinium dithiocarbamate (VI) separated; it recrystallised from water in rhombic tablets which sublimed unchanged at ~200° and melted (sealed tube) at 227° (Found: C, 43·4; H, 7·45; N, 11·1. Calc. for $C_9H_{18}O_2N_2S_2$: C, 43·2; H, 7·2; N, 11·2%). It was best prepared by the action of carbon disulphide on morpholine in acetone, in which it was highly insoluble. This, incidentally, provides a convenient method for the detection of carbon disulphide in small amounts in vapours, etc. When (VI) was dissolved in water and acidified, a white curdy precipitate was produced, which redissolved during one minute.

Action of Tertiary Amines and Aqueous Alkali on (I).—2-Thio-4-methyl-5-thiazolidone (0·73 g.) was kept with triethylamine (0·5 g., 1 equiv.) in acetone (10 c.c.) for 1 hour, and the clear yellow solution acidified with dry hydrogen chloride. Triethylamine hydrochloride was filtered off. and a further crop removed by evaporation and treatment with ether. The filtrate was evaporated, and the residue (0·45 g.), m. p. 116°, washed with water. Crystallisation from benzene gave (I), m. p. 125°, and a small insoluble residue, m. p. 210° (decomp.), soluble in aqueous sodium hydroxide and reprecipitated on acidification.

The thiazolidone (I) (1·0 g.) was heated under reflux with pyridine (10 c.c.) for 30 minutes, and the resulting gel diluted with methanol to granulate the *polymer*, which contracted considerably when dried at 100° (Found: C, 47·2; H, 7·2; N, 17·4; S, 0·38%). It was a white powder, m. p. ~290°, insoluble in common solvents. (I) (1·0 g.) was destroyed when heated under reflux with methanol (10 c.c.) for 1 hour; the product was oily and readily soluble in organic liquids.

Saturated solutions of (I) in 0·34N-barium hydroxide and 0·5N-potassium hydroxide deposited colourless needles, m. p. 126°, of (I) after a short while (see p. 643). An attempt was made to follow the decomposition of (I) with alkali, by keeping the pH constant at 9 with small progressive additions of 0·34N-barium hydroxide. The readings became variable and unreliable after about 30 minutes, but it was established that about 33% of (I) decomposed during the first hour.

We are grateful to Sir Ian Heilbron, D.S.O., F.R.S., for his interest and encouragement, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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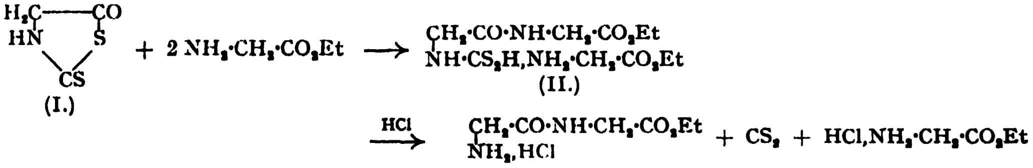
125. *Studies in the Azole Series. Part XXVII. A New Method of Peptide Synthesis: Glycyl Peptides.*

By A. H. Cook and A. L. Levy.

2-Thio-5-thiazolidone (I) is a useful reagent for the addition of a glycyl residue to the ester of an α-amino-acid or peptide in a single operation. Coupling takes place in the presence of a tertiary base and the product is released by acidification. In this way, for example, the polyglycine esters up to pentaglycine ethyl ester hydrochloride (III) have been prepared stepwise from glycine ester, in good yields at each stage. α-Amino-acid or peptide esters are very suitable for partition chromatography on paper, and may be revealed by the use of ninhydrin in the usual way.

In Part XIX (Billimoria and Cook, *J.*, 1949, 2323) anhydrocarboxyglycine was shown to be too reactive to allow a useful synthesis of glycylglycine ester. In Part XXV, however (*J.*, 1950, 637) a method for the controlled preparation of glycine amides from the dithio-analogue, 2-thio-5-thiazolidone (I), was established in principle, using morpholine as a model base. In the present paper, the application of this reaction to α-amino-esters is described and shown to provide a ready method for the synthesis of glycyl peptides.

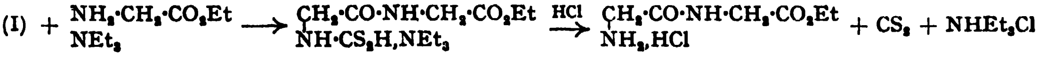


$$\text{(I)} + 2\,NH_2\cdot CH_2\cdot CO_2Et \longrightarrow \begin{matrix}CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et\\ NH\cdot CS_2H,NH_2\cdot CH_2\cdot CO_2Et\end{matrix}\ \text{(II.)}$$

$$\xrightarrow{HCl} \begin{matrix}CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et\\ NH_2,HCl\end{matrix} + CS_2 + HCl,NH_2\cdot CH_2\cdot CO_2Et$$

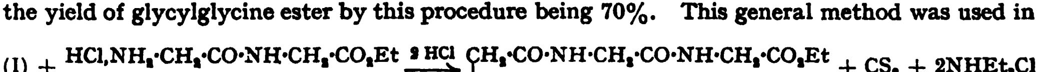
When 2-thio-5-thiazolidone (I) was treated with two equivalents of glycine ethyl ester in ethyl acetate, the dithiocarbamate (II) separated as an uncrystallisable oil. In chloroform, however, a clear solution resulted and, when this was treated directly with dry hydrogen chloride and evaporated, a mixture of glycine ester hydrochloride and glycylglycine ester hydrochloride was obtained. A better procedure was to conduct the initial condensation in ethanol, acidification of the clear solution with ethanolic hydrogen chloride causing separation of the crude peptide ester hydrochloride in 78% yield. This was freed from glycine ester hydrochloride by one crystallisation from ethanol, the yield of pure material being then 50%.

Glycylglycine ethyl ester (two equivalents) was added to one equivalent of (I) in ethanol, followed almost immediately by two equivalents of ethanolic hydrogen chloride, which caused rapid separation of almost pure triglycine ester hydrochloride in 96% yield, the filtrate yielding crystals of the dipeptide ester hydrochloride on storage. Treatment of (I) with one equivalent only of glycine ester gave a poor yield of impure dipeptide. However, (I) reacted smoothly with a mixture of one equivalent each of glycine ester and triethylamine in chloroform, and acidification then caused pure glycylglycine ester hydrochloride to separate in 57% yield, triethylamine hydrochloride being soluble in chloroform.



$$\text{(I)} + \begin{matrix}NH_2\cdot CH_2\cdot CO_2Et\\ NEt_3\end{matrix} \longrightarrow \begin{matrix}CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et\\ NH\cdot CS_2H,NEt_3\end{matrix} \xrightarrow{HCl} \begin{matrix}CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et\\ NH_2,HCl\end{matrix} + CS_2 + NHEt_3Cl$$

The peptide ester hydrochlorides may conveniently be converted into the bases *in situ* by treating the thiothiazolidone directly with an amino-ester hydrochloride and two equivalents of triethylamine. Thus, (I) in ethanol gave an 86% yield of the tripeptide ester hydrochloride, the yield of glycylglycine ester by this procedure being 70%. This general method was used in subsequent experiments. When it was applied to the above tripeptide ester hydrochloride, tetraglycine ethyl ester hydrochloride was obtained in a yield of 88%. The latter gave a strong biuret reaction, unlike the starting material and lower peptides. This fact is responsible for the trivial name " biuret base " given by Curtius (*Ber.*, 1883, 16, 755; 1904, 37, 1286) to the tetrapeptide ester, which he prepared by keeping glycine ester for several weeks in ahydrous ether. Curtius recorded for the hydrochloride m. p. 192—193°, whereas Fischer (*Ber.*, 1904, 37, 2504), who prepared the compound by esterification of tetraglycine, gave a value of 212—214°. We have confirmed the latter figure and shown by paper chromatography that the material prepared



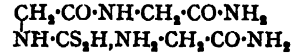
$$\text{(I)} + \begin{matrix}HCl,NH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et\\ 2NEt_3\end{matrix} \xrightarrow{2\,HCl} \begin{matrix}CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et\\ NH_2,HCl\end{matrix} + CS_2 + 2NHEt_3Cl$$

by tetramerising glycine ester contains a small proportion of penta- and hexa-peptides which depress the melting point.

$$\mathrm{HCl,NH_2{\cdot}[CH_2{\cdot}CO{\cdot}NH]_4{\cdot}CH_2{\cdot}CO_2Et} \qquad \text{(III.)}$$

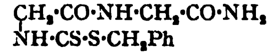
Conversion of " biuret base " hydrochloride into the *pentapeptide ethyl ester hydrochloride* (III) in a yield of 85% was achieved in a similar fashion, except that 92% methanol was required to dissolve the more complex starting material. It has previously been demonstrated with the model tripeptide synthesis, that the method was still applicable in the presence of 75% ethanol, though the yield dropped to 64% as compared with 86% in the anhydrous solvent, a result which was not unexpected in view of the known fission of *N*-dithiocarboxyglycine amides by aqueous acids.

The general procedure was applicable also to amino-esters other than glycine, in both their optically active and their racemic forms. Thus when L-tyrosine methyl ester was treated with (I) and triethylamine in chloroform, addition of dry hydrogen chloride gave *glycyl-L-tyrosine methyl ester hydrochloride* in a yield of 50%. This yield dropped to 20% when two equivalents of triethylamine were present, but increased slightly to 57% with 1·5 equivalents each of (I) and triethylamine. Similarly, DL-phenylalanine ester gave glycyl-DL-phenylalanine methyl ester hydrochloride in a yield of 30% which was not improved by several variations in the reaction conditions. When 2-thio-4-phenyl-5-thiazolidone (Billimoria and Cook, *loc. cit.*) became available, it was condensed with glycylglycine ester hydrochloride, giving 37% of *α-phenylglycylglycine ethyl ester hydrochloride*.



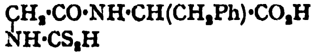
$$\begin{array}{l}\mathrm{CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH_2}\\ \mathrm{NH{\cdot}CS_2H,NH_2{\cdot}CH_2{\cdot}CO{\cdot}NH_2}\end{array}$$

(IV.)



$$\begin{array}{l}\mathrm{CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH_2}\\ \mathrm{NH{\cdot}CS{\cdot}S{\cdot}CH_2Ph}\end{array}$$

(V.)



$$\begin{array}{l}\mathrm{CH_2{\cdot}CO{\cdot}NH{\cdot}CH(CH_2Ph){\cdot}CO_2H}\\ \mathrm{NH{\cdot}CS_2H}\end{array}$$

(VI.)

The reality of the dithiocarbamate intermediates postulated above was shown by the isolation of (IV), characterised as the *benzyl* ester (V), after reaction of (I) with glycine amide in ethanol.

Unlike most free peptides, the peptide ester hydrochlorides which resulted from the synthesis were highly crystalline substances with sharp melting or decomposition points, which were depressed strongly by the presence of impurities. In many cases they proved more suitable than the free peptides for analysis by partition chromatography on paper (for a review, see Consden, *Nature*, 1948, **162**, 359) because their higher R_F values led to much more satisfactory separation. This was well exemplified by the above polyglycine ester hydrochlorides and the corresponding free peptides obtained by hydrolysis. With the salts the paper chromatograms, with butanol–acetic acid as the mobile phase, showed a regular decrease in the R_F value by a factor of about ¾ for each additional glycine residue, except the first. A similar relation holds in the other polyglycine series mentioned below. By paper chromatography, it was shown that glycine was produced when (I) was warmed to 70° in water, whereas in more concentrated solution loss of carbon disulphide was accompanied also by the formation of lower polyglycines and the presence of those up to pentaglycine was demonstrated. In a similar fashion, the lower five polyglycyl-peptides of L-tyrosine, methionine, norvaline, phenylalanine, and *iso*leucine were produced by heating (I) with the appropriate amino-acid in water, or better, glacial acetic acid, and readily identified by paper chromatography. The R_F values of a number of amino-acids, glycyl-peptides, and their esters in butanol–acetic acid are collected at the end of the Experimental section.

In the case of alanine, methionine, and valine methyl esters, reaction with (I) under the standard conditions mentioned above failed to yield crystalline dipeptide ester hydrochlorides, though their formation was clearly shown by paper chromatography. This analysis also indicated the formation of several other ninhydrin-reactive substances in small amounts from such syntheses; glycine methyl ester hydrochloride and the dimeride of (I) (Part XXV, *loc. cit.*) were identified. The former was produced by reaction of (I) with the methanol used as solvent in that case, and the latter by the action of triethylamine, though the emergence of peptides in substantial yield from such reactions shows that dimerisation is slow compared with the ring-opening of (I) by amines. In such cases where the esters were not readily crystallised, the method could still be used to provide the desired peptide by hydrolysis of the crude ester and chromatography of the product on a column of cation-exchange resin (see the succeeding paper). This was illustrated by the case of glycylvaline, which was thus obtained crystalline.

Finally, it has been shown that (I) can also be utilised preparatively to give a glycyl-peptide by reaction with a free amino-acid. Thus, rapid fission occurred when (I) was shaken with a solution of phenylalanine in two equivalents of sodium hydroxide, and on acidification a heavy yellow oil was produced which was probably the dithiocarbamic acid (VI). When this was dissolved in acetone, glycyl-DL-phenylalanine rapidly crystallised in 25% overall yield. The isolation of (VI) appeared to result from the hydrophobic character of the phenylalanine residue.

While the classical methods of peptide synthesis are too well known to require additional mention here, the use of anhydro-*N*-carboxyamino-acids bears a close relation to the present method and deserves therefore to be briefly reviewed. The first such compound, anhydro-*N*-carboxyglycine, was prepared by Leuchs (*Ber.*, 1906, **39**, 857), and some 20 additional members of the series have since been made. Interest has centred mainly on their ability to polymerise to polypeptides of high molecular weight with loss of carbon dioxide (cf., *inter alia*, Astbury, Dalgliesh, Darmon, and Sutherland, *Nature*, 1948, **162**, 596), but the formation of monomeric amides and peptides has been noted on several occasions. Thus anhydro-*N*-carboxy-*N*-phenylglycine was converted into the amide (Leuchs and Manasse, *Ber.*, 1907, **40**, 3235), anilide (Fuchs, *Ber.*, 1922, **55**, 2943), ethylamide, methylanilide, and piperidide of *N*-phenylglycine (Wessely, *Z. physiol. Chem.*, 1925, **146**, 72) and the corresponding peptides with glycine, glycine ester, and tyrosine ester (*idem, ibid.*). Anhydro-*N*-carboxy-β-phenylalanine gave the anilide (Curtius and Sieber, *Ber.*, 1922, **55**, 1543), amide, ethylamide, and 2 : 2-diethoxyethylamide of phenylalanine (Wessely and Sigmund, *Z. physiol. Chem.*, 1926, **157**, 91), and with glycine and glycylglycine gave the peptides phenylalanylglycine and phenylalanylglycylglycine; with tyrosine ester the peptide ester cyclised to phenylalanyltyrosine anhydride, and with aniline, phenylalanylphenylalanylanilide was isolated (*idem, ibid.*). By reaction of anhydro-*N*-carboxy-β-phenylalanine with aniline and methylaniline picrates, the corresponding phenylalanine amide picrates were obtained, and the same technique was also used successfully for anhydro-*N*-carboxyglycine (Wessely and John, *Monatsh.*, 1927, **48**, 11). The latter anhydride has recently been condensed with morpholine and glycine ester at a low temperature (Billimoria and Cook, *loc. cit.*). Reaction of D-anhydro-*N*-carboxyalanine with 2 equivalents of L-histidine ester in chloroform has yielded D-alanyl-L-histidine (31%), after hydrolysis (Hunt and Du Vigneaud, *J. Biol. Chem.*, 1938, **125**, 699).

In these simple cases, polymerisation is minimised by the effect of three factors, separately or in combination: (1) The loss of carbon dioxide is slow compared with the initial ring-opening reaction; this is ensured either by the effect of substituents in the oxazolid-dione ring (*e.g.*, with the derivatives of alanine and phenylalanine; cf. also 2-thio-5-thiazolidones) or by cooling (*e.g.*, with anhydrocarboxyglycine). (2) The initiating amine is usually a stronger base than that produced by loss of carbon dioxide (*e.g.*, with anhydro-*N*-carboxy-*N*-phenylglycine). (3) Where the initiating amine is a weaker base than that produced by loss of carbon dioxide, the latter is preferentially engaged by an acid, *e.g.*, picric acid, included in the medium. The use of 2-thio-5-thiazolidones described in the present paper entails the use of stable crystalline compounds which give rise to little or no complications of polymerisation.

EXPERIMENTAL.

Reaction of (I) *with Glycine Ethyl Ester.*—(*a*) 2-Thio-5-thiazolidone (0·68 g.) was suspended in chloroform (15 c.c.). Addition of glycine ethyl ester (1·0 g., 2 equivs.) caused dissolution with evolution of heat. Dry hydrogen chloride was passed in, the solution evaporated, and the residue treated with ethanol, to give crude glycylglycine ester hydrochloride, which had m. p. 185—186° after a further crystallisation from ethanol.

(*b*) 2-Thio-5-thiazolidone (0·66 g.) in ethanol (10 c.c.) was treated with glycine ethyl ester (1·0 g., 2 equivs.), followed after 10 minutes by 10N-ethanolic hydrogen chloride (1 c.c., 2 equivs.). Glycylglycine ethyl ester hydrochloride (0·77 g.), m. p. 155—170°, separated on cooling in ice, and was recrystallised from ethanol to give the pure compound (0·5 g.), m. p. 183—184°.

Reaction of (I) *with Glycylglycine Ethyl Ester.*—Glycylglycine ethyl ester hydrochloride (Fischer and Fourneau, *Ber.*, 1901, **34**, 2868) (8·0 g.) was suspended in chloroform and shaken rapidly with potassium hydroxide (2·5 g.) in water (3 c.c.). The chloroform was twice replaced, and the combined extracts dried (Na_2SO_4) and evaporated, to yield the free base (4·5 g.), m. p. 87—88°. The base (1·6 g., 2 equivs.) in ethanol (10 c.c.) was added to 2-thio-5-thiazolidone (0·66 g.) in ethanol (15 c.c.), and the solution acidified with 10N-ethanolic hydrogen chloride (1 c.c., 2 equivs.) after 10 minutes at room temperature. The mixture set to a solid mass of triglycine ethyl ester hydrochloride (1·2 g., 96%), m. p. 213° (decomp.) (lit., m. p. 214°), and overnight the filtrate deposited crystals of the dipeptide ester hydrochloride (0·3 g.), m. p. 180—181°, a further crop being obtained by addition of ether.

Reaction of (I) *with Glycine Ester and Triethylamine.*—2-Thio-5-thiazolidone (0·66 g.) was suspended in chloroform (10 c.c.) and cooled to 0°. A mixture of glycine ethyl ester (0·51 g., 1 equiv.) and triethylamine (0·5 g., 1 equiv.) in chloroform (2 c.c.) was added during 15 minutes, and the solution kept for a further 15 minutes in the ice bath. Acidification with 10N-ethanolic hydrogen chloride (1 c.c., 2 equivs.) then gave glycylglycine ethyl ester hydrochloride (0·57 g., 57%), m. p. 182—183°, which was collected after 2 hours at 0°. From the filtrate, overnight, a small quantity (0·05 g.) of material, m. p. 208°, was obtained.

Glycylglycine Ethyl Ester Hydrochloride.—A warm suspension of glycine ethyl ester hydrochloride (0·7 g.) in ethanol (5 c.c.) containing triethylamine (1·0 g., 2 equivs.) was added to 2-thio-5-thiazolidone (0·66 g.) in ethanol (5 c.c.), and the mixture acidified with 10N-ethanolic hydrogen chloride after 15 minutes. The product (1·17 g.), collected after 1 hour at 0°, was recrystallised from ethanol (containing free hydrogen chloride) to give somewhat impure glycylglycine ethyl ester hydrochloride (0·68 g., 70%), m. p. 162—169°.

Triglycine Ethyl Ester Hydrochloride.—2-Thio-5-thiazolidone (10 g.) was added to a mixture of glycylglycine ethyl ester hydrochloride (15 g., 1 equiv.) and triethylamine (15 g., 2 equivs.) in ethanol (150 c.c.), and the clear solution acidified with 5N-ethanolic hydrogen chloride (30 c.c., 2 equivs.). On seeding of the solution, triglycine ethyl ester hydrochloride (16·7 g., 86%) separated as a mass of plates, m. p. 213—214° (decomp.), which, recrystallised from water–acetone, had m. p. 216—217° (decomp.).

(I) (0·66 g., 1 equiv.) in 75% ethanol (10 c.c.) was treated with a solution of glycylglycine ester (0·80 g., 1 equiv.) and triethylamine (0·50 g., 1 equiv.) in 75% ethanol (5 c.c.), and acidified after a few minutes with 10N-ethanolic hydrogen chloride. Triglycine ester hydrochloride (0·8 g., 64%), m. p. 217—218° (decomp.), was then caused to separate by addition of ether. In an otherwise similar experiment, acidification was effected with 50% hydrogen bromide in acetic acid, whereupon the beautifully crystalline ***triglycine ethyl ester hydrobromide*** separated on scratching, and was recrystallised from ethanol, whereupon it had m. p. 191° (Found : C, 32·5; H, 5·5. $C_8H_{16}O_4N_3Br$ requires C, 32·2; H, 5·4%). The compound was soluble in methanol and insoluble in acetone.

Tetraglycine Ethyl Ester Hydrochloride.—Triglycine ethyl ester hydrochloride (12·6 g.) was shaken with triethylamine (10 g., 2 equivs.) in ethanol (400 c.c.) and filtered from a small quantity (0·8 g.) of undissolved ester. 2-Thio-5-thiazolidone (6·6 g., 1 equiv.) was added, and the solution seeded and acidified at once with ethanolic hydrogen chloride (2 equivs.), whereupon tetraglycine ethyl ester hydrochloride (12·3 g.) rapidly separated. A further 0·5 g. (total yield, 88%) of crystalline material was deposited from the filtrate. The main crop contained a small quantity of bound sulphur, which could be removed by dissolution in boiling water, filtration, and crystallisation of the " biuret base " hydrochloride as lustrous platelets, m. p. 213—214° (decomp.) (8·75 g.), by addition of ethanol containing a little free hydrogen chloride.

" Biuret base " hydrochloride prepared according to Curtius (*loc. cit.*) had m. p. 195—199° (decomp.), raised to 199—202° by one crystallisation from aqueous ethanol. With aqueous picric acid it gave a picrate, m. p. 222° (decomp.) (lit., m. p. 189°), not depressed on admixture with the picrate of " biuret base " prepared by the present method. Paper chromatography of the Curtius " biuret base " hydrochloride on Whatman No. 1 paper, with butanol–acetic acid as the mobile phase, gave three spots of R_F 0·19, 0·11, and 0·065, respectively; the first two corresponded to the known tetra- and penta-peptide ester hydrochlorides of glycine, and the third was presumed to be due to the hexapeptide.

When the above pure hydrochloride was dissolved in the minimum volume of water, addition of triethylamine caused precipitation of the free " biuret base," which crystallised well from methanol in clusters of needles or platelets. It dissolved when suspended in methanol, and the solution was treated with hydrogen bromide in acetic acid, whereafter addition of ether caused separation of ***tetraglycine ethyl ester hydrobromide***, which recrystallised from ethanol as plates (Found : C, 33·8; H, 5·4. $C_{10}H_{19}O_5N_4Br$ requires C, 33·8; H, 5·4%).

Pentaglycine Ethyl Ester Hydrochloride.—Tetraglycine ethyl ester hydrochloride (5·0 g., 1 equiv.) was dissolved in water (12·5 c.c.) and solutions of triethylamine (3·2 g., 2 equivs.) in methanol (95 c.c.) and finely powdered 2-thio-5-thiazolidone (2·11 g., 1 equiv.) in methanol (65 c.c.) were rapidly added, a clear, pale pink solution resulting. Acidification with 5N-ethanolic hydrogen chloride (7 c.c.), seeding, and scratching gave the required pentapeptide ester hydrochloride (4·6 g.), m. p. 227—228° (decomp.), and a further 0·4 g. (total yield, 85%), m. p. 224° (decomp.), separated from the filtrate on storage. ***Pentaglycine ethyl ester hydrochloride*** recrystallised from aqueous acetone or aqueous methanol containing a little free hydrogen chloride as laths, m. p. 236—237° (decomp.) (Found : C, 39·5; H, 6·0. $C_{12}H_{22}O_6N_5Cl$ requires C, 39·2; H, 6·0%). With aqueous picric acid, it yielded a picrate, m. p. 230—231° (decomp.).

*Glycyl-*L*-tyrosine Methyl Ester Hydrochloride.*—L-Tyrosine methyl ester (0·97 g.) was boiled with chloroform (20 c.c.) and then rapidly cooled, triethylamine (0·5 g., 1 equiv.) followed by 2-thio-5-thiazolidone (0·66 g., 1 equiv.) was added, and the whole was shaken. After 4 hours the purple solution was acidified with 10N-ethanolic hydrogen chloride (2 c.c.), and the product (0·7 g., 50%), m. p. 204° (decomp.), which was at first gummy but later crystalline, filtered off and washed with chloroform and then acetone. ***Glycyl-*L*-tyrosine methyl ester hydrochloride*** recrystallised best from methanol–ethyl acetate. It had m. p. 223 (decomp.) (Found : C, 49·4; H, 5·7; N, 9·95. $C_{12}H_{17}O_4N_2Cl$ requires C, 49·9; H, 5·9; N, 9·7%).

L-Tyrosine methyl ester (5·0 g.) was boiled with chloroform (150 c.c.) for 10 minutes, and filtered hot. To the warm filtrate was added triethylamine (3·75 g., 1·5 equivs.) and 2-thio-5-thiazolidone (5·0 g., 1·5 equivs.), and the mixture was kept overnight at room temperature. Dry hydrogen chloride was passed in until the solution was saturated, and the sticky gum which had separated rubbed with portions of chloroform to remove triethylamine hydrochloride and crystallised (3·8 g.), m. p. 217° (decomp.), by addition of acetone. The decanted chloroform slowly deposited a further 0·4 g. (total yield, 57%) of product. Recrystallisation from methanol–ethyl acetate gave the pure peptide ester hydrochloride (3·0 g.), m. p. 222—223° (decomp.).

*Glycyl-*DL*-phenylalanine Ethyl Ester Hydrochloride.*—DL-Phenylalanine methyl ester hydrochloride 1·08 g.) was dissolved in chloroform (75 c.c.) containing triethylamine (1·0 g., 2 equivs.), and the whole added to a suspension of 2-thio-5-thiazolidone (0·66 g., 1 equiv.) in chloroform (5 c.c.). Reaction appeared slower than usual, and after 30 minutes at room temperature the solution was acidified with 10N-ethanolic hydrogen chloride (2 c.c.), seeded, and cooled in ice for 4·5 hours. The glycyl-DL-phenylalanine methyl ester hydrochloride which separated (0·39 g., 30%) was washed with acetone and had m. p. 166°, undepressed on mixing with a sample made by esterifying glycyl-DL-phenylalanine (Leuchs and Suzuki, *Ber.*, 1904, **37**, 3313). The yield was not improved by addition of triethylamine to the other two components during 1 hour, by the alternative use of pyridine, or by reaction of the thiazolidone with 2 equivs. of phenylalanine ester free base.

DL-*Phenylglycylglycylglycine Ethyl Ester Hydrochloride.*—A solution of 2-thio-4-phenyl-5-thiazolidone (0·52 g.) in ethanol (10 c.c.) was treated with a mixture of glycylglycine ethyl ester (0·4 g., 1 equiv.) and triethylamine (0·25 g., 1 equiv.) in ethanol (10 c.c.). An immediate red colour was produced, which soon faded. After 25 minutes, the solution was acidified with 10N-ethanolic hydrogen chloride (1·5 c.c.) and cooled in ice with addition of a little ether. DL-*Phenylglycylglycylglycine ethyl ester hydrochloride* (0·3 g., 37%) was collected after 30 minutes, washed with acetone, and recrystallised from methanol–ether or –acetone in small laths, m. p. 239—240° (decomp.) (Found : C, 50·3; H, 5·9. $C_{14}H_{20}O_4N_3Cl$ requires C, 51·0; H, 6·1%). The above thiazolidone afforded a crystalline triethylamine salt with the base in acetone, which regenerated the thiothiazolidone on acidification in water.

Reaction of (I) *with Glycine Amide.*—Glycine amide (1·2 g.) in ethanol (50 c.c.) was added with stirring at 0° during 45 minutes to a solution of 2-thio-5-thiazolidone (1·05 g.) in ethanol (70 c.c.). The dithiocarbamate separated as a slightly pink, deliquescent solid. A portion was shaken with benzyl chloride in ether–water (8 hours) to give N-*dithiocarbobenzyloxyglycylglycine amide*, m. p. 116—118° (hydrate ?) which recrystallised from ethyl acetate in rosettes of blades, m. p. 136° (Found : C, 49·1; H, 5·3; N, 13·7. $C_{12}H_{15}O_2N_3S_2$ requires C, 48·5; H, 5·05; N, 14·1%). When the above dithiocarbamate was dissolved in water and acidified with dilute hydrochloric acid, 2-thio-5-thiazolidone was produced in poor yield. When (I) was treated with glycine amide in acetone, the dithiocarbamate was superficially similar, but with benzyl chloride gave a low yield of a derivative, m. p. 195—196°.

Reaction of (I) *with Alanine Methyl Ester.*—Alanine methyl ester hydrochloride (1·4 g.) and triethylamine (2·02 g., 2 equivs.) were dissolved in methanol (15 c.c.), 2-thio-5-thiazolidone (1·33 g., 1 equiv.) was added, and the whole shaken. Heat was evolved and a pink solution obtained. This was acidified with 7N-methanolic hydrogen chloride (4 c.c.) and evaporated, and triethylamine hydrochloride (2·2 g.) removed by careful addition of acetone in which it was insoluble. The filtrate was analysed by paper chromatography (see final section), and shown to contain glycylalanine ester (yellow ninhydrin spot, R_F 0·37) as the main constituent, together with a little alanine ester (R_F 0·46), an unknown substance (R_F 0·55), and a glycine derivative (yellow ninhydrin spot, R_F 0·11). On storage overnight, the last substance separated in small amount, and had m. p. 195 °(decomp.); it was sparingly soluble in ethanol. The filtrate was evaporated, the soluble hydrochlorides were extracted into water, and the bases liberated with potassium carbonate. Treatment with ethereal picric acid gave a small quantity of picrate, m. p. 93—125°, which could be recrystallised from ethanol and on chromatography on paper separated into a picric acid spot and a ninhydrin-reactive spot (R_F 0·55). It would thus appear to be the picrate of the unknown compound above.

Reaction of (I) *with Methionine Methyl Ester.*—2-Thio-5-thiazolidone (0·33 g.) was added to a mixture of methionine methyl ester hydrochloride (0·50 g., 1 equiv.) and triethylamine (0·50 g., 2 equivs.) in methanol (5 c.c.) and the whole shaken. After 20 minutes, 7N-methanolic hydrogen chloride (1 c.c.) was added, and the mixture evaporated and treated twice with acetone to give crops (total, 0·55 g.) of triethylamine hydrochloride. Paper chromatography of the filtrate showed it to be a mixture of the required glycyl-DL-methionine methyl ester hydrochloride (R_F 0·55) with unchanged methionine ester hydrochloride (R_F 0·75), 2-thio-5-thiazolidone dimer (reddish-purple spot, R_F 0·39), and glycine. Both the thiazolidone and diaminoacetoacetic acid to which it readily gives rise yield a characteristic reddish-purple ninhydrin spot at R_F 0·27 (glycine, 0·065), preceded by a " tail " in the former instance.

Reaction of (I) *with Valine Methyl Ester.*—2-Thio-5-thiazolidone (0·67 g.) was added to a mixture of valine methyl ester hydrochloride (0·84 g., 1 equiv.) and triethylamine (1·02 g., 2 equivs.) in dry methanol (10 c.c.) and the whole shaken. After 15—30 minutes, the reddish-brown solution was acidified with 7N-methanolic hydrogen chloride (2 c.c.) and evaporated to a gum, from which triethylamine hydrochloride was removed by two treatments with acetone. The filtrate contained largely glycyl-DL-valine methyl ester hydrochloride (R_F 0·66), together with valine ester (R_F 0·76) and a small amount of a substance having R_F 0·36 (yellow spot), together with a trace of glycine (R_F 0·10). On evaporation and treatment with ethyl acetate, the substance having R_F 0·36 separated; recrystallised from ethanol–ether, it had m. p. 178° (decomp.); analysis showed it to be glycine methyl ester hydrochloride (Found : C, 29·3; H, 6·4; N, 11·0. Calc. for $C_3H_8O_2NCl$: C, 28·7; H, 6·4; N, 11·15%). The filtrate, which darkened when kept overnight, did not yield the required peptide in crystalline condition.

The above synthesis was also carried out in chloroform solution, and in this case paper-chromatographic analysis of the product, after removal of the triethylamine hydrochloride, showed that glycine methyl ester was absent but that two other impurities (R_F 0·40 and 0·46) were present. The former had the characteristic reddish-purple ninhydrin reaction of the dimer of (I), and the latter was a glycyl derivative (yellow ninhydrin spot) the constitution of which is unknown. The oily glycylvaline ester hydrochlorides from this and the preceding experiment were combined and hydrolysed with 2N-sodium hydroxide. The solution was acidified with acetic acid and evaporated to dryness, whereafter treatment with ethanol caused separation of sodium chloride, which was removed. The filtrate was evaporated, dissolved in water, and chromatographed on a column of " Zeokarb 215 " as described in the succeeding paper. Crystalline glycyl-DL-valine, m. p. 239° (decomp.), chromatographically pure, was obtained in rather poor yield.

Reaction of (I) *with Phenylalanine.*—DL-Phenylalanine (0·83 g.) was dissolved in N-sodium hydroxide (10 c.c., 2 equivs.), 2-thio-5-thiazolidone (0·67 g., 1 equiv.) added, and the whole shaken to give a clear yellow solution. After 20 minutes this was acidified with concentrated hydrochloric acid (2·0 c.c.), and the heavy yellow oil which separated was removed and washed with water. Dissolution in acetone and seeding caused glycyl-DL-phenylalanine (0·28 g., 25%), m. p. 266° (decomp.), to separate rapidly; it recrystallised from aqueous ethanol in clusters of needles, m. p. 267° (decomp.). Similarly, when glycyl-DL-phenylalanine (0·96 g.) was shaken with a solution of potassium hydroxide (0·48 g.) in water (3·5 c.c.) and carbon disulphide (0·4 g.) for 2·2 hours, and the resulting clear reddish-orange solution acidified with concentrated hydrochloric acid, a heavy yellow oil was produced, which yielded glycylphenylalanine when dissolved in acetone.

Paper Chromatography.—For this work, unidimensional, descending chromatograms were run on Whatman No. 1 paper, with butanol–acetic acid (BuOH : AcOH : H_2O = 4 : 1 : 5) as the mobile phase. This solvent gave sharper spots and a cleaner paper, and was more pleasant to handle than phenol. Temperatures varied from about 15° to 25° on different occasions. The R_F values varied considerably with different papers, temperatures, etc., though their relative values remained more constant. Glycine was therefore arbitrarily selected as standard with R_F 0·10, and run with every chromatogram, the observed R_F values of other substances being computed proportionally. This correction was of less value with substances of high R_F values, which remained more constant under different experimental conditions and was therefore not applied in such cases (see tables). All spots were yellow initially with ninhydrin, but changed to the usual purple colour after keeping for some hours. In practice all the various crops of crystals, filtrates, etc., were analysed chromatographically though only certain significant determinations are reported. Values found are given in the annexed tables.

R_F *Values in butanol–acetic acid.*

	Free acid.	Me ester hydro-chloride.	Et ester hydro-chloride.	Amide.
Glycine	0·10	0·36	0·37	—
Alanine	0·18	0·46	—	—
Valine	0·42	0·53	—	—
Leucine	0·57	—	—	—
Norleucine	0·96	—	—	0·43
Phenylalanine	0·50	0·66	—	—
Methionine	0·33	0·52	—	—
Tyrosine	0·54	0·50	—	0·31
Glutamic acid	0·14	—	0·69 *	—
Arginine	0·07	—	—	—

	Free acid.	Me ester hydro-chloride.	Et ester hydro-chloride.
Glycylglycine	0·096	0·25	0·335
Triglycine	0·078	—	0·25
Tetraglycine	0·053	—	0·18
Pentaglycine	0·033	—	0·12
Glycylalanine	0·37	0·26	—
Glycylvaline	0·37	0·46	—
Glycylphenylalanine	0·36	0·52	—

Diglycylphenylalanine	0·30
Triglycylphenylalanine	0·23
Tetraglycylphenylalanine	0·18
Pentaglycylphenylalanine	0·14
Hexaglycylphenylalanine	0·11
Glycylmethionine methyl ester hydrochloride	0·38
Glycyl-leucine	0·42
Diglycyl-leucine	0·33
Triglycyl-leucine	0·25
Tetraglycyl-leucine	0·21
Pentaglycyl-leucine	0·155
Glycyltyrosine methyl ester hydrochloride	0·48
Glycylnorleucine	0·38
Diglycylnorleucine	0·30
Triglycylnorleucine	0·23
Tetraglycylnorleucine	0·17
Pentaglycylnorleucine	0·12
Polymer (MeOH, EtOH, pyridine) of (I)	0·52

* Diethyl ester hydrochloride.

We express our gratitude to Sir Ian Heilbron, D.S.O., F.R.S., for his very helpful interest, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

Imperial College of Science and Technology,
S. Kensington, London, S.W.7.

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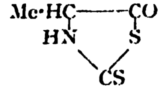
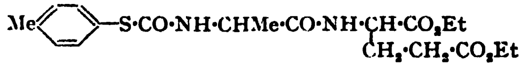
126. *Studies in the Azole Series. Part XXVIII. A New Method of Peptide Synthesis: Alanyl-peptides.*

By A. H. Cook and A. L. Levy.

2-Thio-4-methyl-5-thiazolidone (I) has been used to provide alanyl-peptides in three different ways: (*a*) by the " ester " method described in the preceding paper, which gives lower yields than in the analogous glycine series; (*b*) by reaction with amino-acids in alkaline solution, followed by acidification with weak acids, preferably at an elevated temperature; and (*c*) by direct combination with amino-acids in hot acetic acid. Mixtures of the required peptide and its component amino-acids which result from (*b*) and (*c*) are conveniently separated on a column of cation-exchange resin.

When attempts were made to apply the general synthetic method described in the preceding paper for glycyl-peptides to the corresponding alanine derivative (I), the greater stability of (I) foreshadowed by earlier studies with model bases (Cook, Heilbron, and Levy, Part XXVI, *J.*, 1950, 642) precluded complete success. Thus, with alanine ester, the formation of alanylalanine ester was shown by the isolation of alanine anhydride but the yield was small. As with 2-thio-5-thiazolidone, a better result was obtained by coupling with a dipeptide ester, and alanylglycylglycine methyl ester hydrochloride was obtained in 40% yield by reaction with glycylglycine methyl ester and triethylamine in chloroform and then adding dry hydrogen chloride. This was later improved to 66% by acidifying with ethanolic acetic acid, followed by hydrogen chloride. As a model for the reaction with simple α-amino-esters, the condensation of (I) with ethyl L-glutamate was studied; DL-alanyl-L-glutamic ester so obtained was isolated as its crystalline derivative, *ethyl* DL-N-[(p-*tolylthio*)*formyl*]*alanyl*-L-*glutamate* (II), in a yield of 18%. The same overall yield also resulted from the four-stage synthesis: alanine methyl ester hydrochloride ⟶ *N*-[(*p*-tolylthio)formyl]alanine methyl ester ⟶ *N*-[(*p*-tolylthio)-formyl]alanine ⟶ *N*-[(*p*-tolylthio)formyl]alanyl chloride ⟶ (II) (cf. Ehrensvärd, *Nature*, 1947, **157**, 500; Levy, *J.*, in the press).


(I.)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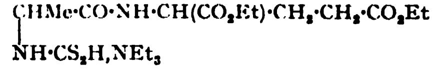
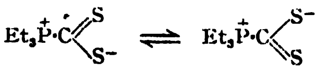
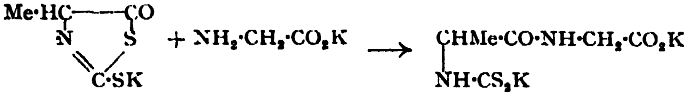

$$\begin{array}{l}\mathrm{CHMe{\cdot}CO{\cdot}NH{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et}\\ |\\ \mathrm{NH{\cdot}CS_2H,NEt_3}\end{array}$$
(III.)

$Ph{\cdot}NH{\cdot}NH{\cdot}CS_2H$
(IV.)


(V.)

It appeared from the work described in Part XXVI (*loc. cit.*) that opening of the ring in (I) by amines proceeded with excellent yield, but that acidification tended to cause reversion to (I) in substantial amount, even under anhydrous conditions. Some experiments were therefore carried out to see if carbon disulphide could be eliminated from (III) without the use of acids. It was shown in Part XXVI (*loc. cit.*) that the morpholine analogue of (III) readily lost its carbon disulphide as the highly insoluble morpholinium salt of 4-dithiocarboxymorpholine, but attempts to obtain this compound from (III) by treatment with two equivalents of morpholine were not successful. It is known that phenylhydrazine forms the stable compound (IV) with carbon disulphide (Fischer, *Annalen*, 1877, **190**, 114), but preliminary experiments with 2-thio-5-thiazolidone indicated the consumption of four equivalents of phenylhydrazine and did not show promise. Triethylphosphine and carbon disulphide form a red addition compound (Hofmann, *Ber.*, 1880, **13**, 1732), which may be formulated as the hybrid (V). It was hoped that the basic character of triethylphosphine would allow it to replace triethylamine in (III), when it might then detach carbon disulphide to give (V) and the required dipeptide ester. Indeed, when (I) was treated with equivalent amounts of ethyl glutamate and triethylphosphine in ethyl acetate, (V) was deposited in 50% of the theoretically possible amount during two hours, but the filtrate failed to yield (II) on treatment with tolyl chloro(thiolformate). However, replacing the triethylamine by triethylphosphine in the synthesis of glycylglycine ester discussed in the preceding paper resulted in a slight increase in yield, though the yield of glycyl-L-tyrosine ester was unaffected by a similar change. Some further properties of (V) are mentioned in the Experimental section.

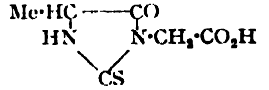
As basic methods for removing carbon disulphide were unpromising, further study was given to acidification procedures. Following the action of boron trifluoride–ether on (III), (II) was obtained in a yield of 14% but, from the action of oxalic acid, only triethylamine oxalate could be isolated. Very slow acidification of (III) with hydrogen chloride in chloroform or in water (cf. Part XXVI, *loc. cit.*) did not yield any (II) on suitable treatment with *p*-tolyl chloro-(thiolformate).

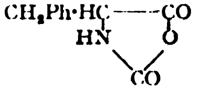

(VI.) (VII.)

In view of these difficulties the possibility of effecting a useful interaction between 2-thio-5-thiazolidones and free amino-acids or peptides in aqueous solution was explored. The thiothiazolidone (I) was dissolved in one equivalent of N-potassium hydroxide to give a solution of the monopotassium salt (VI) (pH 8·7), and a solution of glycine in one equivalent of N-potassium hydroxide added. The pH at once rose to 10·52 and then fell rapidly as the ring opened to give (VII), no further change appearing to take place after 10 minutes (pH 6·0). This fall in pH was to be expected during ring-fission, for not only is a strong base thereby consumed, but an acid ($^-NH{\cdot}CS_2H$) is liberated which is considerably stronger than the original mercaptothiazolone. As in the procedure developed for the model ammonium dithiocarbamate in Part XXVI (*loc. cit.*), the solution was titrated with N-hydrochloric acid during two hours, allowing time for loss of carbon disulphide to occur between each addition of acid. The " steps," however, were far less pronounced than in the model case, and (I) began to separate at pH 4·9 after only 15% of the theoretical quantity of acid had been added, and continued till the end (pH 2·9), a yield of 68% being recovered. Paper chromatography of the filtrate showed that a little alanylglycine had been produced, together with much glycine and a moderate quantity of alanine. In an otherwise similar experiment, where an equivalent of boric acid was present, a 77% recovery of (I) was obtained and no alanylglycine could be detected in the filtrate. The absence of any unchanged (VI) in the solutions before acidification was shown by their stability to carbon dioxide, which liberates (I) from (VI), but not from (VII). In a slow titration of the crystalline barium salt of *N*-dithiocarboxyglycine with N-hydrochloric acid, carbon disulphide was liberated but the " steps " of pH drift were much less definite than with the ammonium salt of *N*-dithiocarboxyalanine amide; clearly the electrometric method is not so indicative of dithiocarbamic acid rupture in the case of peptides. A more promising result was obtained by acidifying (VII) with two equivalents of acetic acid, whereby the yield of (I) fell to 31% (45% on another occasion), paper chromatography showing that alanylglycine had been synthesised in fair quantity, though it was contaminated with glycine and alanine. Propionic acid gave a 28% recovery of (I), and very slow acidification with acetic acid yielded only a trace, but in each case the alanylglycine produced was mixed with its component amino-acids. The isolation of alanylglycine from such solutions by crystallisation proved difficult, owing to its tendency to form mixed crystals with the alanine and the glycine also present. This analytical problem was overcome, however, by " chromatography " on a column of the sulphonic acid-containing exchange-resin " Zeokarb 215 " (see Partridge and Westall, *Biochem. J.*, 1949, **44**, 418); the amino-acids were preferentially eluted by 0·1N-ammonia, followed immediately by the pure peptide. An attempt to use the column of resin to acidify (VII) and separate the products at the same time was not successful, for copious crystallisation of (I) took place and interfered with the flow of liquid.

Even milder conditions of acidification were achieved by opening the barium salt of (I) with barium glycine and decomposing the resulting barium salt of (VII) with carbon dioxide at 100°. Barium carbonate was precipitated, though incompletely even after 20 minutes, but the alanylglycine was once more contaminated with alanine and glycine, chromatography on " Zeokarb 215 " giving the crystalline peptide. When (VII) was treated with aqueous lead acetate, a yellow lead salt was clearly precipitated, which however with hydrogen sulphide yielded lead sulphide and the usual mixture of alanine, glycine, and peptide. Boiling the lead salt with water gave black lead sulphide, but the product was soluble in ethanol and was probably the 2-thiohydantoin (VIII) formed from an intermediate *iso*thiocyanate.

(VIII.)





(IX.)

A variation on the above techniques consisted in shaking a mixture of (I) and glycine with two equivalents of aqueous sodium hydrogen carbonate [whereupon the solids dissolved with evolution of carbon dioxide (neither, separately, gave carbon dioxide with the hydrogen carbonate)] and acidifying with two equivalents of acetic acid at 70°. Carbon disulphide was freely liberated, and no (I) separated on cooling. The method was also applicable to 2-thio-5-thiazolidone, which was in this way coupled with valine to give crystalline glycylvaline.

A third approach to the synthesis of alanyl-piptides from (I) was initiated by the observation that boiling equivalent quantities of (I) and glycine in water for a few moments led to substantial synthesis of alanylglycine. It was, of course, mixed with alanine and glycine, but no higher peptides were present, and the yield as judged from the relative intensity of the ninhydrin spots after chromatography of a sample of the product on paper was of the same order as that produced in the more elaborate experiments already described. When (I) was heated alone with water, it was hydrolysed completely to alanine without formation of any polymeric material. The effect of other solvents, and of different proportions of the reactants on the peptide synthesis was examined; the best procedure was to boil equimolecular amounts of (I) and glycine in acetic acid, which gave a mixture of alanylglycine and glycine (free from alanine). On a preparative scale, alanylglycine resulted in 48% yield from this reaction after " chromatography " on " Zeokarb 215." The analogous condensation with amino-acids other than glycine was less ready, though the synthesis of alanyl-glycylglycine, -alanine, -valine, and -arginine was demonstrated by paper chromatography. The direct method can also be used for α-amino-esters, and the syntheses of alanylglycine ester and alanylvaline ester by heating the components in acetic acid was established.

It was interesting to note that when anhydrocarboxyphenylalanine (IX) (Leuchs and Geiger, *Ber.*, 1908, **41**, 1721; Levy, *Nature*, in the press) was heated with glycine, tetraglycine, alanine, or valine in acetic acid, only the lower two or three polyphenylalanyl peptides were produced without any further polymerisation.

A list of R_F values of alanyl- and phenylalanyl-peptides is given at the end of the Experimental section.

EXPERIMENTAL.

Reaction of (I) *with Alanine Ester.*—2-Thio-4-methyl-5-thiazolidone (0·74 g.), DL-alanine methyl ester hydrochloride (0·70 g., 1 equiv.), and triethylamine (1·0 g., 2 equivs.) were dissolved in ethanol (10 c.c.) and kept at room temperature for 45 minutes. The solution was acidified with ethanolic hydrogen chloride and cooled in ice, and a crop of triethylamine hydrochloride removed; the filtrate was evaporated to dryness and a further crop precipitated by adding acetone. The filtrate was evaporated, and the residue rubbed with ethyl acetate to remove any thiothiazolidone. The remaining material was treated with saturated sodium hydrogen carbonate and extracted with chloroform, whereafter evaporation gave a basic-smelling oil which was kept at 100° in a vacuum to afford crystals of alanine anhydride, m. p. 275°.

Reaction of (I) *with Glycylglycine Methyl Ester.*—2-Thio-4-methyl-5-thiazolidone (0·73 g.), glycylglycine methyl ester hydrochloride (0·91 g., 1 equiv.), and triethylamine (1·0 g., 2 equivs.) were kept for 1·5 hours in chloroform (10 c.c.), and the solution was saturated with dry hydrogen chloride. A little ether was added. A semi-crystalline sludge obtained after 2 days was treated with ethanol-acetone to yield crude alanylglycylglycine methyl ester hydrochloride (0·5 g., 40%), m. p. 127—148°, which recrystallised from ethanol to give a product m. p. 153°, which was not depressed on admixture with material made according to Pacsu and Wilson (*J. Org. Chem.*, 1942, **7**, 126) and gave a single spot (R_F 0·25) on a paper chromatogram.

The same starting materials were kept for 50 minutes in ethanol (10 c.c.), acetic acid (0·65 c.c.) was added, and after 1·25 hours dry hydrogen chloride (2 equivs.) was passed in. Sufficient ethanol was added to re-dissolve a little triethylamine hydrochloride which separated, and the solution seeded with L-alanylglycylglycine methyl ester hydrochloride and kept overnight. The product which crystallised (0·84 g., 66%) had m. p. 158°, after contracting at 146°, and was essentially the same as the alanylglycylglycine methyl ester hydrochloride described above.

Ethyl DL-N-[(p-*Tolylthio*)*formyl*]*alanyl*-L-*glutamate.*—(*a*) 2-Thio-4-methyl-5-thiazolidone (0·73 g.) in chloroform (20 c.c.) was kept with ethyl L-glutamate (1·0 g., 1 equiv.) and triethylamine (0·5 g., 1 equiv.) for 1 hour. Dry hydrogen chloride was passed in, the solution concentrated in a vacuum, and the syrup dissolved in ethyl acetate, to which a little ether was then added. The solution was extracted with water (5 × 1—2 c.c.), and the aqueous phase treated with solid potassium carbonate at 0° and extracted with ether (3 times), some insoluble oil being rejected. The ethereal solution was dried ($MgSO_4$) and treated with *p*-tolyl chloro(thiolformate) (Levy, *J.*, in the press) until precipitation of triethylamine hydrochloride was complete. After 30 minutes, this was washed with water and with 2N-hydrochloric acid, dried, and evaporated to yield *ethyl* DL-N-[(p-*tolylthio*)*formyl*]*alanyl*-L-*glutamate* (0·4 g., 18%), m. p. 94°, which was recrystallised from ether without change of m. p. (Found: C, 56·8; H, 6·4; N, 6·4. $C_{20}H_{28}O_6S$ requires C, 56·6; H, 6·6; N, 6·6%).

(*b*) Alanine nitrile (Part XXVI) (23 g.) was added cautiously at 0° to a saturated solution of hydrogen chloride in methanol (120 c.c.), and kept overnight at room temperature. Ammonium chloride was filtered off, and the DL-alanine methyl ester hydrochloride (20·3 g.) crystallised [m. p. 155° (decomp.)] by adding ether to the filtrate. A further crop (10·2 g.; total yield, 66%), m. p. 152° (decomp.), was obtained by dilution with ethyl acetate and storage overnight at 0°. The ester hydrochloride (1·4 g.) in dry pyridine (3 c.c.) was treated, with cooling, with a solution of *p*-tolyl chloro(thiolformate) (1·87 g.) in pyridine (2 c.c.), and the whole stored overnight at 0°. The mixture was diluted with chloroform and extracted with 2N-hydrochloric acid, and the chloroform layer dried and evaporated, to yield *N*-[(*p*-tolylthio)formyl]alanine methyl ester (2·0 g., 80%), m. p. 83°. This ester (7·0 g.) was heated under reflux with acetic acid (25 c.c.) and concentrated hydrochloric acid (25 c.c.) for 15 minutes, water (25 c.c.) was added, and the mixture cooled to room temperature, to give *N*-[(*p*-tolylthio)formyl]-alanine (5·5 g., 83%), as flakes of m. p. 163°. This acid (1·2 g.) was boiled with benzene (30 g.), and phosphorus pentachloride (1·2 g.) added to the warm suspension, exothermic dissolution occurring. The benzene solution was concentrated under diminished pressure, and light petroleum added so long as the *N*-[(*p*-tolylthio)formyl]alanyl chloride (0·56 g., 44%) which crystallised [compact rosettes of spears, m. p. 102° (decomp.)] remained free from gum. The chloride (0·26 g.) in dry ether (15 c.c.) was cooled to 0°, and ethyl L-glutamate (0·40 g., 2 equivs.) added; after 1 hour at room temperature, the mixture was extracted with 2N-hydrochloric acid, dried, and evaporated to yield ethyl DL-*N*-[(*p*-tolylthio)formyl]alanyl-L-glutamate (0·31 g., 72%), m. p. 88°.

Experiments with Triethylphosphine.—Triethylphosphine (Hibbert, *Ber.*, 1906, **39**, 161) (0·59 g.) and ethyl glutamate (1·0 g.) in ethyl acetate (5 c.c.) were added to 2-thio-4-methyl-5-thiazolidone (0·73 g.) in ethyl acetate (5 c.c.). After 2 hours at room temperature, the deep-red prisms of triethylphosphine-carbon disulphide (0·5 g.) were removed, and the filtrate concentrated to small bulk. Treatment with *p*-tolyl chloro(thiolformate) (0·9 g.) and pyridine (2 c.c.), and working up in the usual way, yielded only *p*-tolyl dithiocarbonate, m. p. 95° (Found: C, 65·7; H, 5·4. Calc. for $C_{15}H_{14}OS_2$: C, 65·6; H, 5·14%).

2-Thio-5-thiazolidone (0·67 g.) in chloroform (10 c.c.) was treated with glycine ester (0·51 g., 1 equiv.) and triethylphosphine (0·6 g., 1 equiv.) in chloroform (3 c.c.). After 20 hours at room temperature, addition of ethanolic hydrogen chloride caused glycylglycine ethyl ester hydrochloride (0·72 g., 73%; m. p. 174—176°) to crystallise.

Triethylphosphine–carbon disulphide could be generated from its components in acetic acid, and was decomposed on contact with carbon tetrachloride. When warmed with glycine amide in ethanol, the carbon disulphide was transferred and the amino-amide precipitated as its *N*-dithiocarboxy-derivative. Keeping *a*-aminobenzyl cyanide with triethylphosphine–carbon disulphide in chloroform for 4—5 days caused separation of yellow 2 : 4-dithio-5-phenylhydantoin, m. p. 264—265° (decomp.) (negative glyoxal test; cf. Cook, Heilbron, and Levy, *J.*, 1947, 1598).

Use of Boron Trifluoride.—2-Thio-4-methyl-5-thiazolidone (0·73 g.) in chloroform (10 c.c.) was treated with ethyl L-glutamate (1·0 g., 1 equiv.) and triethylamine (0·5 g., 1 equiv.), and boron trifluoride–ether (1·1 g., 2 equivs.) was added after 1 hour (heat evolved). After a further hour, ethanolic hydrogen chloride was added, and the mixture evaporated to a syrup and mixed with *p*-tolyl chloro(thiolformate) (1·5 c.c.) in pyridine (10 c.c.). After 2·5 hours the solution was concentrated under diminished pressure, dissolved in ethyl acetate, and washed with 2N-sulphuric acid; drying and evaporating then yielded ethyl DL-*N*-[(*p*-tolylthio)formyl]alanyl-L-glutamate (0·3 g., 14%), m. p. 89—91°, after rubbing with a little ether.

Reaction of (I) *with Glycine in Alkaline Solution.*—Powdered 2-thio-4-methyl-5-thiazolidone (0·588 g.) was dissolved in N-potassium hydroxide (4·0 c.c., 1 equiv.) (pH then 8·7), and a solution of glycine (0·3 g., 1 equiv.) in N-potassium hydroxide (4·0 c.c.) added. The resulting pH changes were as follows:

pH	10·52	10·26	9·88	9·48	8·82	7·54	6·96	6·70
Time (mins.)	0	0·5	1	1·5	2	2·5	3	3·5
pH	6·55	6·44	6·38	6·27	6·18	6·14	6·05	6·03
Time (mins.)	4	4·5	5	6	7	8	10	11

The solution was then titrated slowly with N-hydrochloric acid (8·0 c.c.) during about 2 hours, the pH changes being followed for an average of 3 minutes after each addition. Initially, the rise was 0·2 pH unit during this period. (I) began to crystallise after 1·2 c.c. of acid had been added, the pH drift at this point being 0·15 unit in 3 minutes but becoming less as the titration proceeded. Finally, the mixture was extracted with ether, and the dried extracts were evaporated to yield (I) (0·40 g., 68%).

Experiment with Barium Glycine-N-*dithiocarboxylate.*—Glycine (1·5 g.) and barium hydroxide octahydrate (6·3 g.) were dissolved in water (15 c.c.) (warming), and shaken overnight with carbon disulphide (1·5 c.c.). On filtration of the solution from a little insoluble material, the required salt crystallised in dense, colourless prisms, m. p. above 300°. When titrated with N-hydrochloric acid (2 equivs.) during 1 hour, carbon disulphide was liberated, and the pH fell from 4·35 to 1·70. However, the rise in pH following each addition of acid was not marked, being about 0·2 unit in 3 minutes.

Use of Acetic Acid and a Cation-exchange Column.—2-Thio-4-methyl-5-thiazolidone (2·95 g.) was added to a solution of glycine (1·5 g., 1 equiv.) in N-potassium hydroxide (40 c.c., 2 equivs.), and the whole shaken. After 2 hours, acetic acid (2·4 g.) was added, and the 2-thio-4-methyl-5-thiazolidone which slowly separated (1·17 g.) was collected after an additional 2 hours. Extraction of the filtrate with ethyl acetate gave a further 0·15 g. of (I) (total recovery, 45%). The aqueous layer was evaporated to dryness in a vacuum, and the residue digested with several portions of hot ethanol to remove potassium acetate (the extract yielded a little glycine on cooling). The remaining material was dissolved in water (15 c.c.) (it contained glycine, alanylglycine, and alanine—paper chromatography) and run on to a column (25 cm. high in a 50-c.c. burette) of " Zeokarb 215 " (~10 g., sieved to be retained between 40 and 60 B.S.S.). The " Zeokarb " was prepared for use by running through it (*a*) sodium chloride solution, (*b*) 4N-hydrochloric acid, and (*c*) distilled water. The zone of adsorption of the amino-acids and peptide was clearly visible, as the resin had changed from orange to yellow-brown, and the column was run with distilled water until this zone had grown to its full length. Development was then continued with 0·1N-ammonia, and the effluent collected in 5-c.c. fractions when a positive ninhydrin test was first given. The pH changes in the effluent were not a reliable guide to its composition, so 3 μl. of each fraction were run on a paper chromatogram for analysis. The first 7 fractions contained glycine and alanine, the eighth glycine, alanylglycine, and alanine, and the ninth to eleventh the peptide, with rapidly diminishing amounts of its component amino-acids, the last being pure alanylglycine. Fractions 10 and 11 were evaporated to dryness, and the residue crystallised from 50% ethanol-acetone to give pure alanylglycine (about 0·2 g.).

Use of Barium and Lead Salts.—Glycine (1·5 g.) in 0·34N-barium hydroxide (120 c.c.) was shaken for 45 minutes with 2-thio-4-methyl-5-thiazolidone (2·95 g.), and the solution (pH 8) treated with a stream of carbon dioxide (pH then 7), raising the temperature slowly. Precipitation of barium carbonate did not begin until the solution was almost boiling; this temperature was maintained for 45 minutes. The carbonate was removed (1·95 g.), and the filtrate (which still contained Ba^{++}) run on to a column of " Zeokarb 215 " similar to that used above, except that resin retained between 100 and 120 B.S.S. was used. The overlap of amino-acids and peptide was less in this case, and 5 fractions containing pure alanylglycine were obtained on elution with ammonia, which yielded the solid peptide on evaporation.

(I) (0·735 g.) was shaken with glycine (0·375 g.) in N-potassium hydroxide (10 c.c.), and the resulting solution treated with aqueous lead acetate. The derivative was precipitated cleanly, yellow at first, but becoming almost white when the lead acetate was in excess. A portion of this lead derivative was suspended in water and treated with hydrogen sulphide. It dissolved to give a deep-brown solution, from which lead sulphide was precipitated after addition of a little acetic acid and boiling. The colourless filtrate contained glycine, alanylglycine, and alanine, as shown by paper chromatography. Another portion of the lead derivative was boiled with water for 15 minutes, being completely decomposed to give lead sulphide. The filtrate, however, contained only traces of ninhydrin-reactive materials, and on evaporation the solid residue was completely soluble in hot ethanol.

Use of Sodium Hydrogen Carbonate.—2-Thio-4-methyl-5-thiazolidone (0·73 g.), glycine (0·37 g.), and sodium hydrogen carbonate (0·85 g.) were shaken with water (10 c.c.) for 50 minutes, dissolving with evolution of carbon dioxide. The solution was heated to 70°, acetic acid (0·6 c.c.) was added, and the whole allowed to cool to room temperature. Carbon disulphide separated in small globules, no (I) was recovered, and the solution contained a considerable proportion of alanylglycine, as shown by paper chromatography.

2-Thio-5-thiazolidone (0·67 g.), DL-valine (0·59 g.), and sodium hydrogen carbonate (0·84 g.) were shaken with water (10 c.c.) until dissolved, and no more carbon dioxide was evolved (~20 minutes). The pale pink solution was heated to 80°, and acetic acid (1·5 c.c.) added, after which the solution was evaporated to dryness in a vacuum. The residue was completely soluble in hot ethanol, though on storage overnight with ether a little glycine and valine separated. The filtrate was evaporated, dissolved in water, and run on to a column of "Zeokarb 215" (~15 g.; 100—120 B.S.S.) as in the previous examples. Development with 0·1N-ammonia gave 5 fractions (5 c.c.) containing glycine and valine, followed by 8 of pure glycylvaline. These eight were evaporated to give the solid peptide (0·4 g.), which was rubbed with methanol to remove a little colour and thereafter had m. p. 239° (decomp.).

Reactions with (I) in Acetic Acid.—2-Thio-4-methyl-5-thiazolidone (3·0 g.) and glycine (1·5 g.) were refluxed in acetic acid (85 c.c.) for 5 minutes, and the solvent was evaporated off in a vacuum. The syrupy residue was dissolved in water (10 c.c.), and filtered on to a column (23 × 1·5 cm.) of "Zeokarb 215" (~15 g.; 100—120 B.S.S.), which was washed through with water until acetic acid ceased to emerge and the yellow zone of adsorbed material extended for 18 cm. The column was then washed with 0·1N-ammonia, and the effluent collected in 10-c.c. fractions until the yellow zone reached the foot of the column. Fractions 1—5 contained glycine, 7—9 alanylglycine with diminishing quantities of glycine, and 10—25 alanylglycine, though with nos. 21—25 the ninhydrin spots on the paper chromatogram were slightly elongated, suggesting the presence of an impurity (perhaps alanylalanylglycine). Fractions 10—25 were evaporated to dryness and rubbed with ethanol, to give a slightly deliquescent sample of alanylglycine (1·4 g., 48%). Recrystallisation from 50% ethanol-acetone gave pure material (0·77 g.), m. p. 215° (decomp.).

Syntheses of alanylglycylglycine, etc. (theoretical section), were performed only on a micro-scale (1—2 mg.), with heating for about 1 minute and analysis of a little of the resulting acetic acid solution directly on a paper chromatogram. The new spot, additional to the amino-acid or peptide used, was assumed to be the alanyl derivative. The procedure was similar for the experiments with anhydro-*N*-carboxyphenylalanine, the first spot below the amino-acid being assumed to be the monophenylalanyl derivative, the next the diphenylalanyl, and so on.

R_F *Values of peptides.*

(The paper chromatograms were run with butanol–acetic acid as the mobile phase, as described in Part XXVII, and the R_F values are corrected for glycine = 0·1, unless otherwise stated.)

Alanylglycine	0·15	Phenylalanylglycine	0·34	(G = 0·07)
Alanylglycylglycine	0·107	Diphenylalanylglycine	0·55	,,
Alanylalanine	0·26	Triphenylalanylglycine	0·75	,,
Alanylvaline	0·43	Phenylalanyltetraglycine	0·155	,,
Alanylarginine	0·29	Diphenylalanyltetraglycine	0·37	,,
Alanylglycylglycine methyl ester HCl	0·25	Triphenylalanyltetraglycine	0·54	,,
Alanylvaline methyl ester	0·58	Phenylalanylalanine	0·53	,,
		Phenylalanylvaline	0·575	,,
		Diphenylalanylvaline	0·75	,,

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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127. *The Heats of Hydrolysis of the Benzoyl Halides.*

By A. S. CARSON, H. O. PRITCHARD, and H. A. SKINNER.

From measurements of the heats of hydrolysis of the benzoyl halides in aqueous acetone solutions, the following values (in kcal./mole) were obtained for the heats of formation at room temperature: $Q_f(\text{C}_6\text{H}_5\cdot\text{COCl, liq.}) = 39{\cdot}30$, $Q_f(\text{C}_6\text{H}_5\cdot\text{COBr, liq.}) = 25{\cdot}50$, $Q_f(\text{C}_6\text{H}_5\cdot\text{COI, liq.}) = 12{\cdot}55$.

These data are used to derive provisional values for the bond dissociation energies in a number of benzoyl–X molecules.

THIS paper reports values for the heats of hydrolysis of benzoyl chloride, bromide, and iodide, and is a continuation of studies on the hydrolysis heats of acid halides (Carson and Skinner, *J.*, 1949, 936; Pritchard and Skinner, *J.*, 1950, 272). The heats of hydrolysis of the benzoyl halides have not been measured previously, possibly because the reactions are slow to reach completion in a purely aqueous medium. Thermal difficulties arising from the tardiness of the aqueous hydrolyses may, however, be overcome by using aqueous acetone as the hydrolysis medium (cf. Pritchard and Skinner, *loc. cit.*). In a solvent obtained by mixing 400 c.c. of acetone and 350 c.c. of water, the hydrolysis of benzoyl chloride was virtually complete in 30 minutes, and benzoyl bromide and iodide in the same solvent were hydrolysed in less than 15 minutes.

The heats of hydrolysis can be combined with known thermochemical data to give values for the heats of formation (Q_f) of the benzoyl halides. Apart from a single measurement of the heat of combustion of benzoyl chloride by Rivals (*Ann. Chim. Phys.*, 1897, **7**, 541), corresponding to Q_f(C_6H_5·COCl, liq.) = 53·2 kcals., there are no data in the literature concerning the Q_f of the benzoyl halides.

EXPERIMENTAL.

Preparation of Compounds.—Benzoyl chloride (May and Baker) was purified by fractional distillation under reduced pressure. Benzoyl bromide was a pure Kahlbaum sample. Benzoyl iodide was made by Staudinger's method (*Ber.*, 1913, **46**, 1417), *i.e.*, interaction of hydrogen iodide and benzoyl chloride; the crude product was shaken with mercury to remove traces of free iodine, and purified by careful fractionation under low pressure.

Thermal Measurements.—The heats of hydrolysis were measured by the same technique and apparatus used by Pritchard and Skinner (*loc. cit.*). The *observed* hydrolysis heats (listed in the following tables under $Q_{obs.}$) are the heats of the reactions :

$$C_6H_5\cdot COX\ (liq.) + H_2O(aq.\ acetone) \longrightarrow (C_6H_5\cdot CO_2H + HX)\ (aq.\ acetone) + Q_{obs.} \quad . \quad . \quad (1)$$

and differ from the heats of the purely aqueous hydrolyses (listed under $Q_{aq.}$), *viz.*,

$$C_6H_5\cdot COX\ (liq.) + H_2O\ (liq.) \longrightarrow C_6H_5\cdot CO_2H\ (c) + HX\ (aq.) + Q_{aq.} \quad . \quad . \quad (2)$$

by some small terms arising from the heat of solution and mixing of the benzoic acid and halogen acid in the aqueous acetone. These solution heats were measured separately as required.

In the tables of results, R_i and R_f refer to the initial and final values of the thermistor resistance, and $Q_{aq.}$ gives the heat of reaction (2) when the product is HX ($1000H_2O$).

Heat of hydrolysis of benzoyl halides.

Wt. of acid halide (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (liq.) (kcals.).	Wt. of acid halide (g.).	R_i (ohms).	R_f (ohms).	$Q_{obs.}$ (kcals.).	$Q_{aq.}$ (kcals.).	Q_f (liq.) kcals.).
		Benzoyl chloride.						Benzoyl bromide.			
3·5237	1710·2	1652·0	21·35	24·38	39·27	3·39	1746·8	1696·5	24·9	27·0	25·5
3·7900	1696·1	1634·4	21·23	24·26	39·39	3·0140	1748·8	1703·85	25·03	27·15	25·39
4·2940	1681·0	1611·65	21·34	24·37	39·28	3·5773	1744·0	1691·4	24·80	26·92	25·62
2·1719	1739·0	1701·6	21·36	24·39	39·26	3·0647	1746·0	1700·45	24·98	27·10	25·44
4·2040	1735·1	1663·75	21·31	24·34	39·31	3·0990	1747·0	1701·1	24·88	27·00	25·54
		Mean values	21·32	24·35	39·30			Mean values	24·92	27·04	25·50
					Benzoyl iodide.						
5·4975	1711·7	1649·2	24·29	24·60	12·42	5·3296	1694·0	1635·45	24·00	24·31	12·71
5·9529	1700·15	1633·35	24·17	24·48	12·54	6·0524	1698·3	1631·15	24·24	24·55	12·47
5·1122	1692·2	1635·0	24·14	24·45	12·57	5·7887	1704·6	1640·4	24·11	24·42	12·60
								Mean values	24·16	24·47	12·55

The main reason for the differences between the $Q_{obs.}$ and $Q_{aq.}$ values arises from the negative solution heat (*ca.* −4·80 kcals./mole) of crystalline benzoic acid in the aqueous acetone; the $Q_{aq.}$ values, corresponding to reaction (2), refer to crystalline benzoic acid as one of the reaction products.

The calculated Q_f (liq.) values given in the final columns of the tables are based on assumed values for the heats of formation of the halogen hydracids ("Selected Values of Chemical Thermodynamic Constants," National Bureau of Standards, Washington, 1948) and on Q_f(C_6H_5·CO_2H, c.) = 92·06 kcals./mole (Jessup, *J. Res. Nat. Bur. Stand.*, 1942, **29**, 247). It may be remarked that the Q_f value of 53·2 kcals., derived from Rivals's heat of combustion of benzoyl chloride, corresponds to a heat of hydrolysis ($Q_{obs.}$) of only 7·4 kcals.

DISCUSSION.

The Q_f values obtained from these experiments refer to the *liquid* state at room temperature. Data are not available on the heats of vaporisation of the benzoyl halides, but a rough estimate of these can be made by use of Trouton's rule. The results are summarised below :

	C_6H_5·COCl.	C_6H_5·COBr.	C_6H_5·COI.
Q_f (liq.) (kcals.)	39·30	25·50	12·55
Q_f (gas) (kcals.)	28·9	14·7	1·3
$\lambda_{vap.}$ (assumed) (kcals.)	10·4	10·8	11·2

The Q_f (gas) values may be correlated with the bond dissociation energies D(C_6H_5·CO–X) by the equation

$$D(C_6H_5\cdot CO–X) = Q_f(C_6H_5\cdot COX) - Q_f(X) - Q_f(C_6H_5\cdot CO) \quad . \quad . \quad . \quad . \quad (3)$$

where the terms in Q_f are heats of formation from elements in standard states, and $D(C_6H_5\cdot CO{-}X)$ is the heat of the reaction $C_6H_5\cdot CO + X \longrightarrow C_6H_5\cdot COX$. The term $Q_f(C_6H_5\cdot CO)$ in equation (3) cannot be determined directly, but can be evaluated if both $D(C_6H_5\cdot CO{-}X)$ and $Q_f(C_6H_5\cdot COX)$ are known for *one* specific $C_6H_5\cdot COX$ compound. In this event, equation (3) can be generally applied to determine D(benzoyl–X) in other benzoyl derivatives.

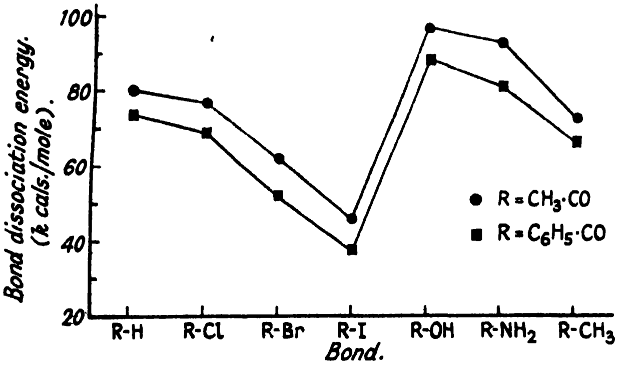
Apart from the kinetic studies of Butler and Polanyi (*Trans. Faraday Soc.*, 1943, **39**, 19) on the pyrolytic decomposition of benzoyl iodide, there are no experimental data from which D values in benzoyl–X can be assessed. Butler and Polanyi gave $D(C_6H_5\cdot CO{-}I) = 43{\cdot}9$ kcals., but this result was not claimed to be of high accuracy. In general, the D(R–I) values given by Butler and Polanyi seem to be accurate within limits of ±5 kcals., and for the purpose of the present paper we shall adopt a value of $D(C_6H_5\cdot CO{-}I) = 42$ kcals. ($\pm x$), where x is probably less than 5 kcals. This provisional $D(C_6H_5\cdot CO{-}I)$ value corresponds to Q_f(benzoyl) $= -15{\cdot}2 \pm x$ kcals., which, substituted into equation (3), leads to the following D values in the listed benzoyl–X compounds :

Bond.	Q_f (gas).	Q_f (X).	$D(C_6H_5\cdot CO{-}X)$ ($\pm x$).	Bond.	Q_f (gas).	Q_f (X).	$D(C_6H_5\cdot CO{-}X)$ ($+x$).
$C_6H_5\cdot CO{-}H$ ...	11·2 [a]	−52·0	78·4 *	$C_6H_5\cdot CO{-}OH$	68 [a]	−10·0	93·2 *
$C_6H_5\cdot CO{-}Cl$ ...	28·9 [b]	−29·0	73·1	$C_6H_5\cdot CO{-}NH_2$	30 [c]	−41·0 [d]	86·2 *
$C_6H_5\cdot CO{-}Br$ ...	14·7 [b]	−26·7	56·6	$C_6H_5\cdot CO{-}CH_3$	24 [c]	−32·1	71·3 *
$C_6H_5\cdot CO{-}I$ ...	1·3 [b]	−25·5	42	$C_6H_5\cdot CO{-}C_6H_5$	−13 [e]	−69·8	72 *

[a] Based on data listed by Wheland ("The Theory of Resonance," John Wiley, 1944). [b] This research. [c] Kharasch (*J. Res. Nat. Bur. Stand.*, 1929, **2**, 407). [d] Szwarc (*J. Chem. Physics*, 1949, **17**, 505). [e] Beckers (*Bull. Soc. chim. Belg.*, 1931, **40**, 518); Neumann and Volker (*Z. physikal. Chem.*, 1932, **161**, *A*, 33).

* Asterisked values are doubtful because of uncertainties in the heats of formation Q_f (gas).

The value given for $D(C_6H_5\cdot CO{-}H)$ is a relatively " low " value for a C–H bond dissociation energy. Compared with the C–H bonds in ethylene or benzene, both of which are of the same sp^2–s hybrid type, $D(C_6H_5\cdot CO{-}H)$ is smaller by some 20 or more kcals. The weakness of the benzoyl–H bond is strongly suggestive of a powerful resonance stabilisation in the benzoyl radical.



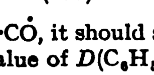
Roberts and Skinner (*Trans. Faraday Soc.*, 1949, **45**, 339) commented on the weakness of the C–H bond in acetaldehyde, $D(CH_3\cdot CO{-}H) \approx 80$ kcals., and attributed this to a stabilisation in the acetyl radical by a 3-electron bond resonance, *i.e.*, (I) $\rightleftharpoons$ (II). In so far as a resonance stabilisation of this type occurs in $CH_3\cdot\dot{C}O$, it should similarly be present in the benzoyl radical, and from this point of view the low value of $D(C_6H_5\cdot CO{-}H)$ should be compared with the low value of $D(CH_3\cdot CO{-}H)$. Indeed, one might expect the $C_6H_5\cdot\dot{C}O$ radical to be resonance-stabilised to a greater extent than $CH_3\cdot\dot{C}O$, in that the excited structures of the types (III), (IV), and (V) in relation to $C_6H_5\cdot\dot{C}O$ are probably more significant than the structures $H^{\cdot}CH_2{=}C{=}O$ in relation to $CH_3\cdot\dot{C}O$.

$$CH_3{-}\dot{C}{=}\ddot{O}$$

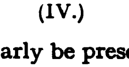
(I.)

$$CH_3{-}\underset{-}{\ddot{C}}{=}\underset{+}{\dot{O}}$$

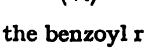
(II.)



(III.)

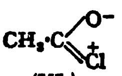


(IV.)



(V.)

In the figure, bond-dissociation energies in a series of benzoyl–X and acetyl–X compounds



$\mathrm{CH_3{\cdot}C(\text{–}O^-)(\text{=}\overset{+}{Cl})}$

(VI.)

are plotted together,* to bring out their close similarity in respect of varying X. The present values do not correspond to a strictly constant difference, ΔD, where $\Delta D = D(\mathrm{CH_3{\cdot}CO\text{–}X}) - D(\mathrm{C_6H_5{\cdot}CO\text{–}X})$, although these differences are approximately equal. Some of the D values are, however, based on not very reliable combustion-heat data, and most involve uncertainties of the order ±1 or ±2 kcals. in the heats of vaporisation, so that the trends in ΔD may be partly obscured by errors in the data we have used. Nevertheless, the data are sufficient to show that the factors influencing the strength of acetyl–X bonds are similarly operative in benzoyl–X. For example, if one accepts the importance of back-co-ordination, as represented by the resonance structure (VI) in acetyl chloride, it would seem to be no less important in benzoyl chloride.

The authors thank Professor M. G. Evans, F.R.S., for his interest in this work, and Mr. T. Charnley for some valuable assistance in the preparation of benzoyl iodide. One of them (H. O. P.) thanks the D.S.I.R. for a maintenance grant.

MANCHESTER UNIVERSITY. [*Received, November 18th, 1949.*]

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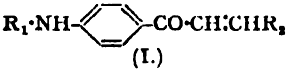
128. *Studies on Antibiotics. Part IV.*† *Substitued ω-Phenylsulphonylacetophenones, Bisphenylthio- and Bisphenylsulphonyl-alkane Derivatives.*

By F. BERGEL, A. L. MORRISON, and H. RINDERKNECHT.

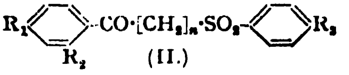
In continuation of previous work (Rinderknecht, Ward, Bergel, and Morrison, *Biochem. J.*, 1947, **41**, 463), the preparation of substances containing a combination of substituted benzoyl and phenylsulphonyl groups was undertaken with the aim (unfulfilled) of finding effective antibacterial agents. Thus various aromatic β-keto-sulphones (II; $n = 1$), β-bisthio-compounds (III), and β-disulphones (IV) were synthesised.

IN Part II of our series "Studies on Antibiotics" (*Biochem. J.*, 1947, **41**, 463) we showed that benzoylacrylic acid and its 4-chloro- and 2 : 4-dichloro-derivatives possessed marked activities *in vitro* against Gram-positive and Gram-negative organisms. We deduced in agreement with Geiger and Conn (*J. Amer. Chem. Soc.*, 1945, **67**, 112) that the presence of the grouping –CO–C=C– might be a pre-requisite for such antibacterial properties (cf. also Geiger, *Arch. Biochem.*, 1948, **16**, 423). In continuation of this work we prepared some time ago *p*-acetamidobenzoylacrylic acid (I; $R_1 = Ac$, $R_2 = CO_2H$) (cf. B.P. 588,108/1944) which we failed to hydrolyse to the 4-amino-compound. Since then, two groups of American workers, Papa, Schwenk, Villani, and Klingsberg (*J. Amer. Chem. Soc.*, 1948, **70**, 3356) and Cramer, Schroeder, Moran, Nield, Edwards, Sarowsky, and Puetzer (*J. Amer. Pharm. Assoc., Sci. Edn.*, 1948, **37**, 439), announced the preparation of this acetamido-compound among other derivatives of benzoylacrylic acid. We wished to replace the carboxyl group of benzoylacrylic acid by another structure and synthesised, independently of Marrian, Russell, and Todd (*J.*, 1947, 1419) 4 : 4′-diaminochalkone (I; $R_1 = H$, $R_2 = p\text{-}NH_2{\cdot}C_6H_4$); but unlike these authors we prepared the starting material, 4-nitro-4′-aminochalkone, directly from *p*-aminoacetophenone and *p*-nitrobenzaldehyde under acidic conditions and then reduced it with stannous chloride.

As the next step, we attempted the synthesis of substances containing both substituted benzoyl and phenylsulphonyl groups, being prompted by the results of Kuhn *et al.* (*Ber.*, 1942, **75**, 711; 1943, **76**, 405).



(I.)



(II.)

Whilst we failed to synthesise amino-substituted α-keto-sulphones (II; $n = 0$) in spite of the claims by Kohler and Macdonald (*Amer. Chem. J.*, 1899, **22**, 225) for unsubstituted ones, we succeeded in making a number of representatives of β-keto-sulphones (II; $n = 1$) by treating sodium acetamido- or acetamidomethyl-benzenesulphinate with ω-chloroacetophenone substituted by acetamido-, hydroxy-, or chloro-groups. In this we followed Troeger and Beck (*J. pr. Chem.*, 1913, [ii], **87**, 289) who prepared several arylsulphonylacetophenones, but none with amino- or aminomethyl substituents. After hydrolysis of the acetamido-derivatives, p-*amino*- (II; $n = 1$, $R_1 = NH_2$, $R_2 = H$, $R_3 = NH_2$), and p-*hydroxy*-ω-p′-*aminophenylsulphonylacetophenone* (II; $n = 1$, $R_1 = OH$, $R_2 = H$, $R_3 = NH_2$) and the corresponding p′-*aminomethyl* compounds ($R_3 = CH_2{\cdot}NH_2$) were obtained. Encouraged by the report on the antitubercular activity of 2 : 4 : 2′ : 4′-tetrachlorobenzophenone (Freedlander, *Proc. Soc. Exp. Biol. Med.*, 1942, **51**, 153; *Amer. Rev. Tubercul.*, 1944, **49**, 543) and the high effect of our 2 : 4-dichlorobenzoylacrylic acid *in vitro*, we added to our list of compounds 2 : 4-*dichloro*-ω-p′-*aminophenylsulphonylacetophenone* (II; $n = 1$, $R_1 = R_2 = Cl$, $R_3 = NH_2$) and the corresponding p′-*aminomethyl* analogue ($R_3 = CH_2{\cdot}NH_2$).

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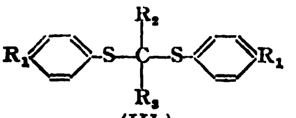
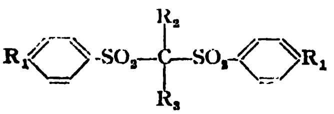
* The benzoyl–X dissociation energies in this figure are based on $x = -5$ kcals., in order to separate the two curves sufficiently to show their form more clearly.

† Part III, *Chem. and Ind.*, 1949, 640.

When, in the general structure (II; $n = 1$), the carbonyl group is exchanged for another sulphonyl group, substances (IV) emerge which can be prepared from β-bisthio-compounds (III) by oxidation. Methods for the synthesis of aliphatic and unsubstituted aromatic representatives of this series were described by Escales and Baumann (*Ber.*, 1886, **19**, 2814), Fromm (*Annalen*, 1889, **253**, 135), and Otto and Muehle (*Ber.*, 1895, **28**, 1121) who either condensed thiols with aldehydes or ketones or treated the sodium salt of thiols with dihalogeno-compounds. Concerning acylamino- or amino-derivatives of aromatic analogues, there are two American papers available: in the earlier, Waldron and Reid (*J. Amer. Chem. Soc.*, 1923, **45**, 2399) claimed the preparation of (III; $R_1 = NH_2$, $R_2 = R_3 = H$) by reduction of the corresponding dinitro-derivative; in the more recent, Cutter, Danielson, and Golden (*ibid.*, 1945, **67**, 1051, published while our investigation was in progress) described the synthesis of bis-*p*-acetamidophenylthiomethane (III; $R_1 = NHAc$, $R_2 = R_3 = H$) from *p*-acetamidothiophenol or its sodium salt with formaldehyde or methylene iodide, respectively. This they also oxidised to (IV; $R_1 = NHAc$, $R_2 = R_3 = H$) which was hydrolysed to the diamino-disulphone (IV; $R_1 = NH_2$, $R_2 = R_3 = H$). In addition to preparing the same compounds, we succeeded in hydrolysing the bis-*p*-acetamidophenylthiomethane to Waldron and Reid's diamino-derivative which formed light ochre-coloured, and not, as they say, red, crystals; we also synthesised certain analogues. For instance, paraldehyde and *p*-acetamidothiophenol gave 1 : 1-*bis*-p-*acetamidophenylthioethane* (III; $R_1 = NHAc$, $R_2 = Me$, $R_3 = H$) which by alkaline hydrolysis, but not by acid (which caused decomposition), yielded the corresponding *diamino*-compound and by oxidation gave (IV; $R_1 = NHAc$, $R_2 = Me$, $R_3 = H$). This sulphone on treatment with alcoholic potassium hydroxide gave 1 : 1-*bis*-p-*aminophenylsulphonylethane* (IV; $R_1 = NH_2$, $R_2 = Me$, $R_3 = H$). By use of acetone or



(III.)



(IV.)

p-nitrobenzaldehyde in the first step of the synthesis 2 : 2-*bis*-p-*acetamidophenylthiopropane* (III; $R_1 = NHAc$, $R_2 = R_3 = Me$) and p-*nitro*-ωω-*bis*-p′-*acetamidophenylthiotoluene* (III; $R_1 = NHAc$, $R_2 = p\text{-}NO_2{\cdot}C_6H_4$, $R_3 = H$), respectively, were obtained. Finally in this group of compounds the use of dichloroacetic acid led to the formation of di-(*p*-acetamidophenylthio)acetic acid (III; $R_1 = NHAc$, $R_2 = CO_2H$, $R_3 = H$) and the corresponding *diamino*-derivative.

When we approached the synthesis of aminomethyl derivatives of (III) and (IV), we found that the preparation of *p*-acetamidomethylthiophenol, wanted as starting material, offered difficulties in view of its great solubility in water. However, three methods were tried which led eventually to success. First, the sodium salt from crude, oily *p*-acetamidomethylthiophenol was condensed with methylene dichloride to give *bis*-p-*acetamidomethylphenylthiomethane* (III; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$). This was oxidised in the usual way to (IV; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$) which hydrolysed with acid to the *bis*-p-*aminomethylphenylsulphonylmethane dihydrochloride* (IV; $R_1 = CH_2{\cdot}NH_2,HCl$, $R_2 = R_3 = H$). Although in our second approach p-*benzamidomethylthiophenol*, unlike the acetyl compound, formed sparingly soluble crystals and could be condensed to give *bis*-p-*benzamidomethylphenylthiomethane* (III; $R_1 = CH_2{\cdot}NHBz$, $R_2 = R_3 = H$), the oxidation of this compound to (IV; $R_1 = CH_2{\cdot}NHBz$, $R_2 = R_3 = H$) was difficult, and further neither the bisthio-compound nor the disulphone could be hydrolysed under alkaline or acidic conditions to the free aminomethyl derivatives. The third and best method used succinimido-derivatives. Succinbenzylamide reacted with chlorosulphonic acid to give p-*succinimidomethylbenzenesulphonyl chloride*, which was reduced in the usual way. p-*Succinimidomethylthiophenol*, thus formed, condensed with formaldehyde, and the product, *bis*-p-*succinimidomethylphenylthiomethane* (III; R_1 = succinimidomethyl, $R_2 = R_3 = H$), was oxidised with hydrogen peroxide to the *disulphone* (IV; R_1 = succinimidomethyl, $R_2 = R_3 = H$). When this bisthio-compound was heated with dilute aqueous sodium hydroxide, and the solution was treated with potassium permanganate, a compound was isolated, very likely the succinamic acid derivative, which, on the one hand, with warm dilute hydrochloric acid gave the succinimido-disulphone described above, and, on the other hand, after prolonged heating with aqueous potassium hydroxide produced *bis*-p-*aminomethylphenylsulphonylmethane*, giving a dihydrochloride and a diacetyl derivative identical with those derived from the disulphone (IV; $R_1 = CH_2{\cdot}NH_2$, $R_2 = R_3 = H$) prepared from crude acetamidomethylthiophenol.

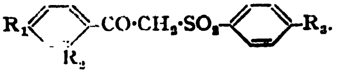
Preliminary bacteriological examination *in vitro* of some of the compounds just mentioned did not disclose any outstanding antibacterial activity.

EXPERIMENTAL.

4 : 4′-*Diaminochalkone* (I; R_1 = H, R_2 = *p*-$NH_2{\cdot}C_6H_4$).—*p*-Nitrobenzaldehyde (4·5 g.) and *p*-aminoacetophenone (4·05 g.) were dissolved in ethanol (100 ml.). After saturation of the solution with gaseous hydrogen chloride under ice-cooling, crystalline material separated overnight and was filtered off and dissolved in 2N-hydrochloric acid (*ca.* 700 ml.). On cooling, the hydrochloride of 4-nitro-4′-aminochalkone crystallised. It was suspended in methanol (100 ml.) and aqueous ammonia was added, whereupon orange-coloured 4-nitro-4′-aminochalkone was obtained; recrystallised from pyridine or chloroform, it had m. p. 221—223° (Found: C, 66·7; H, 4·5; N, 10·1. Calc. for $C_{15}H_{20}O_3N_2$: C, 67·2; H, 4·5; N, 10·4%). This compound (4·0 g.) in saturated alcoholic hydrochloric acid (40 ml.) was reduced with stannous chloride (11·0 g.). When warmed, a yellow solution was obtained which, after storage overnight, deposited a red tin salt. This was dissolved in water and decomposed with a solution of sodium acetate. The diaminochalkone was extracted with butanol and, obtained pure by recrystallising from aqueous acetone, melted at 181—183° (Found: C, 70·4; H, 6·3; N, 11·2. Calc. for $C_{15}H_{14}ON_2,H_2O$: C, 70·4; H, 6·3; N, 10·9%).

ω-p-*Substituted Phenylsulphonylacetophenones* (II; *n* = 1).—A number of compounds of this series was prepared by the general method of Troeger and Beck (*loc. cit.*) from ω-chloroacetophenones and sodium salts of *p*-acetamidophenylsulphinic (cf. *Org. Synth.*, Coll. Vol. I, p. 7) and *p*-acetamidomethylphenylsulphinic acid (cf. F.I.A.T. Final Report No. 915, 52; Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2099). The acetyl derivatives were hydrolysed by heating them to the b. p. with 2N-hydrochloric acid until a clear solution was obtained. Addition of sodium carbonate solution precipitated the free amino-compounds which were recrystallised from the appropriate solvents. These compounds are listed in the table.

ω-Arylsulphonylacetophenones,



R_1.	R_2.	R_3.	M. p.	Solvent for recrystn.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Required, %. C.	Required, %. H.	Required, %. N.
NHAc	H	NHAc	271—274°	A	$C_{16}H_{16}O_5N_2S$	57·6	5·0	—	57·7	4·8	—
NH_2	H	NH_2	225—227	B	$C_{14}H_{14}O_3N_2S$	57·8	4·9	—	58·0	4·8	—
NHAc	H	$CH_2{\cdot}NHAc$	203—205	A	$C_{19}H_{20}O_5N_2S$	59·2	5·3	7·2	58·8	5·2	7·2
NH_2	H	$CH_2{\cdot}NH_2$	185—186	B	$C_{15}H_{16}O_3N_2S$	59·2	5·4	9·3	59·2	5·3	9·2
OH	H	NHAc	235—238	A	$C_{16}H_{15}O_5NS$	—	—	4·3	—	—	4·2
OH	H	NH_2	225—226	C	$C_{14}H_{13}O_4NS$	57·8	4·6	5·2	57·8	4·5	4·8
OH	H	$CH_2{\cdot}NHAc$	168—173	C	$C_{17}H_{17}O_5NS$	58·7	5·2	4·2	58·8	4·8	4·0
OH	H	$CH_2{\cdot}NH_2$	203 *	B	$C_{15}H_{15}O_4NS$	58·8	5·9	4·[illegible]	59·0	4·9	4·6
Cl	Cl	NHAc	164—167	C	$C_{16}H_{13}O_4NCl_2S$	49·8	3·2	—^{a}	49·8	3·4	—^{a}
Cl	Cl	NH_2	172—175	C	$C_{14}H_{11}O_3NCl_2S$	48·5	3·1	4·5	48·8	3·2	4·1
Cl	Cl	$CH_2{\cdot}NHAc$	125—127	C	$C_{17}H_{15}O_4NCl_2S$	51·3	3·3	—^{b}	51·0	3·8	—^{b}
Cl	Cl	$CH_2{\cdot}NH_2$	194—195	D	$C_{15}H_{13}O_3NCl_2S$	50·4	3·7	3·7	50·3	3·6	3·9

* With decomp.
Solvents: A, acetic acid; B, aqueous ethanol; C, ethanol; D, pyridine.
^{a} Found: Cl, 18·3. Required: Cl, 18·4%. ^{b} Found: Cl, 17·9. Required: Cl, 17·8%.

Bis-p-*aminophenylthiomethane* (III; $R_1 = NH_2$, $R_2 = R_3 = H$).—Bis-*p*-acetamidophenylthiomethane (3·8 g.) was hydrolysed by hot 2N-sulphuric acid (100 ml.), the sulphate of the diamine crystallising on cooling. The base itself, obtained by neutralisation with sodium carbonate solution, formed light ochre-coloured crystals when recrystallised from ethanol. It melted at 98—100° (Found: N, 11·1. Calc. for $C_{13}H_{14}N_2S_2$: N, 10·7%).

1 : 1-*Bis*-p-*acetamido- and* -p-*amino-phenylthioethane* (III; R_1 = NHAc or NH_2, R_2 = Me, R_3 = H).—To *p*-acetamidothiophenol (6·68 g.) and chloroform (70 ml.), paraldehyde (0·88 g.) was added and the mixture was saturated with hydrogen chloride. The oily material which separated after 24 hours was treated with boiling water, a white solid being formed. Recrystallisation from ethyl acetate gave pure 1 : 1-*bis*-p-*acetamidophenylthioethane*, m. p. 191—193° (5·9 g.) (Found: N, 7·9. $C_{18}H_{20}O_2N_2S_2$ requires N, 7·8%).

Hydrolysis of the above acetyl derivative (3·4 g.) by refluxing in 10% alcoholic potassium hydroxide solution (34 ml.) for 3 hours yielded only a small amount of the desired material, most of the product being unchanged acetyl derivative. The *bisthio-ethane* was separated from the starting material by dissolution in 2N-hydrochloric acid and then basification, and was obtained pure by recrystallisation from alcohol, whereafter it melted at 81—83° (Found : C, 61·0; H, 5·8; N, 10·5. $C_{14}H_{16}N_2S_2$ requires C, 60·8; H, 5·8; N, 10·1%).

1 : 1-*Bis*-p-*acetamido- and* -p-*amino-phenylsulphonylethane* (IV; R_1 = NHAc or NH_2, R_2 = Me, R_3 = H).—The above bisthio-ethane (III; R_1 = NHAc, R_2 = CH_3, R_3 = H) (5·8 g.) was dissolved in glacial acetic acid (40 ml.), and 60% (w/v) hydrogen peroxide (12 ml.) was added at 40°. After 24 hours at room temperature, the precipitate which had formed was filtered off, washed with water, and recrystallised from 60% aqueous acetic acid (120 ml.), the *diacetyl* compound being obtained pure as a light ochre-coloured compound with m. p. 263—266° (3·7 g.) (Found : N, 6·5. $C_{18}H_{20}O_6N_2S_2$ requires N, 6·6%).

Heating this acetyl compound (2 g.) with a solution of potassium hydroxide (5 g.) in ethanol (14 ml.) and water (7 ml.) under reflux for 4 hours yielded a potassium salt, very sparingly soluble in water, which, on treatment with dilute hydrochloric acid, gave the *diamine*, m. p. 202—204° [recrystallised from ethanol (150 ml.)] (1 g.) (Found : C, 49·9; H, 4·9; N, 8·6. $C_{14}H_{16}O_4N_2S_2$ requires C, 49·4; H, 4·7; N, 8·2%).

2 : 2-*Bis*-p-*acetamidophenylthiopropane* (III; R_1 = NHAc, R_2 = R_3 = Me).—*p*-Acetamidothiophenol (3·4 g.) was condensed with acetone (0·58 g.) in chloroform (35 ml.) by passing in hydrogen chloride. The product which separated overnight was worked up in the usual manner to give the *bisthio-propane*, m. p. 224—225° (recrystallised from ethanol several times) (Found : N, 7·6. $C_{19}H_{22}O_2N_2S_2$ requires N, 7·5%).

p-*Nitro-ωω-bis*-p′-*acetamidophenylthiotoluene* (III; R_1 = NHAc, R_2 = *p*-NO_2·C_6H_4, R_3 = H).—*p*-Acetamidothiophenol (3·4 g.) was condensed with *p*-nitrobenzaldehyde (1·51 g.) in chloroform (150 ml.) in the usual manner by passing in hydrogen chloride. The *bisthio-toluene* was obtained pure by recrystallising it from glacial acetic acid and melted at 221—223° (Found : N, 9·15. $C_{23}H_{21}O_4N_3S_2$ requires N, 9·0%).

Di-(p-*acetamido- and* -p-*amino-phenylthio*)*acetic acid* (III; R_1 = NHAc or NH_2, R_2 = CO_2H, R_3 = H).—Sodium *p*-acetamidothiophenoxide, prepared from sodium (0·7 g.) in ethanol (20 ml.) and the thiol (3·34 g.), was refluxed together with dichloroacetic acid (1·5 g.) for 2 hours. The residue of *bis*-p-*acetamido-acid*, after removal of the solvent by distillation, was treated with dilute hydrochloric acid and water and then sodium hydrogen carbonate, liberated from the resulting sodium salt by dilute hydrochloric acid, and finally recrystallised from ethanol, showing m. p. 230—235° (decomp.) (Found : N, 7·1. $C_{18}H_{18}O_4N_2S_2$ requires N, 7·2%). This derivative (2·5 g.) was hydrolysed by heating it under reflux for 4 hours with 2N-hydrochloric acid (75 ml.). On concentration, a crystalline hydrochloride separated out. This was dissolved in water and the solution neutralised carefully with dilute aqueous ammonia to give the *diamine* which, recrystallised from aqueous alcohol, melted at 117—119° (Found : N, 9·1. $C_{14}H_{14}O_2N_2S_2$ requires N, 9·2%).

Bis-p-*acetamidomethylphenylthiomethane* (III; R_1 = CH_2·NHAc, R_2 = R_3 = H).—*p*-Acetamidomethylbenzenesulphonyl chloride, prepared from *N*-benzylacetamide (48 g.), was dissolved in a mixture of alcohol (30 ml.) and water (100 ml.), zinc dust (100 g.) and concentrated hydrochloric acid (150 ml.) were added in portions with stirring and cooling, and the reaction mixture was finally heated to 80° for 5 minutes. After being cooled the solution was saturated with ammonium sulphate, and the oil which separated was dissolved in amyl alcohol and washed with a small amount of cold water. After removal of the amyl alcohol under reduced pressure, the residue was added to a mixture of ethanol (30 ml.), sodium (1·2 g.), and methylene dichloride (5 g.) and the whole refluxed for 1½ hours. The hot reaction mixture was then centrifuged, and from the separated supernatant layer the *bisthio-methane* crystallised on cooling. It melted at 144—146° when recrystallised from ethanol (Found : C, 61·4; H, 5·7; N, 7·9; S, 17·4. $C_{19}H_{22}O_2N_2S_2$ requires C, 61·0; H, 5·9; N, 7·5; S, 17·1%).

Bis-p-*acetamidomethylphenylsulphonylmethane* (IV; R_1 = CH_2·NHAc, R_2 = R_3 = H).—Oxidation of the above bisthio-methane (0·75 g.) in acetic acid (5 ml.) with 60% hydrogen peroxide (1·5 ml.) in the usual way gave the *disulphone* which, recrystallised from 60% aqueous acetic acid, melted at 236—239° (Found : C, 52·0; H, 5·0; N, 5·9. $C_{19}H_{22}O_6N_2S_2$ requires C, 52·1; H, 5·0; N, 6·4%).

Bis-p-*aminomethylphenylsulphonylmethane Dihydrochloride* (IV; R_1 = CH_2·NH_2, R_2 = R_3 = H).—Hydrolysis of the above acetyl derivative (0·5 g.) with 2N-hydrochloric acid (15 ml.) for 4 hours gave the *dihydrochloride* which, recrystallised from dilute hydrochloric acid, gave white needles which did not melt at 400° but sublimed (Found : C, 42·6; H, 5·0; N, 6·4; Cl, 17·1. $C_{15}H_{18}O_4N_2S_2$,2HCl requires C, 42·2; H, 4·7; N, 6·6; Cl, 16·6%).

p-*Benzamidomethylbenzenesulphonyl Chloride*.—*N*-Benzylbenzamide (100 g.) was gradually added to chlorosulphonic acid (300 ml.) at 15° with stirring. The temperature was then raised to 45° and kept at this level for 1 hour. The reaction mixture was worked up as described for *p*-succinimidomethylbenzenesulphonyl chloride, to give the *sulphonyl chloride*, m. p. 183—184° (after recrystallisation from chloroform–light petroleum) (Found : N, 4·7; Cl, 11·8. $C_{14}H_{12}O_3NSCl$ requires N, 4·5; Cl, 11·3%).

p-*Benzamidomethylthiophenol*.—Reduction of the above sulphonyl chloride (17 g.) with zinc (25 g.) and concentrated hydrochloric acid (55 ml.) (cf. above) yielded the *thiol*, m. p. 134—138° (after recrystallisation from alcohol) (Found : N, 6·0. $C_{14}H_{13}ONS$ requires N, 5·8%).

Bis-p-*benzamidomethylphenylthiomethane* (III; R_1 = CH_2·NHBz, R_2 = R_3 = H).—The above thiol (12·15 g.) and methylene dichloride (4·2 g.) were condensed in methanol (70 ml.) in which sodium (1·08 g.) had been dissolved. The *bisthio-methane*, recrystallised from acetic acid, had m. p. 163—165° (Found : N, 5·6. $C_{29}H_{26}O_2N_2S_2$ requires N, 5·6%).

Bis-p-*benzamidomethylphenylsulphonylmethane* (IV; R_1 = CH_2·NHBz, R_2 = R_3 = H).—The above bisthio-methane (1·25 g.) was oxidised with 60% hydrogen peroxide (2 ml.) in glacial acetic acid (15 ml.), a very large amount of acetic acid being necessary to keep the material in solution. The *product*, which is sparingly soluble in acetic acid, melted at 233—235° (Found : N, 5·0. $C_{29}H_{26}O_6N_2S_2$ requires N, 5·0%).

p-*Succinimidomethylbenzenesulphonyl Chloride.*—To chlorosulphonic acid (140 ml.), succinbenzylimide (14 g.) was added in portions, with stirring, at <10°. The reaction mixture was then heated to 60° for ½ hour and poured on ice. The gummy mass was stirred with two lots of ice-cold water, whereupon it crystallised. Recrystallised from chloroform–light petroleum, it melted at 153—157° (38%) (Found: Cl, 12·8. $C_{11}H_{10}O_4NCl$ requires Cl, 12·4%).

p-*Succinimidomethylthiophenol.*—To the above sulphonyl chloride (6·5 g.) in a mixture of alcohol (12 ml.) and water (7 ml.) were added zinc dust (11 g.) and concentrated hydrochloric acid (20 ml.) during 1 hour with continuous stirring. The reaction mixture was then heated for 2 minutes to 80°. It was then filtered and the filtrate poured into a mixture of ice-water (200 ml.) and concentrated hydrochloric acid (10 ml.). The precipitate was filtered off and dissolved in chloroform (50 ml.), and the chloroform solution washed with water, dried, and evaporated. The residue, recrystallised from alcohol, yielded the pure *thiol* as lemon-yellow crystals, m. p. 119° (68%) (Found: C, 60·0; H, 5·1. $C_{11}H_{11}NS$ requires C, 59·7; H, 5·0%).

Bis-p-*succinimidomethylphenylthiomethane* (III; R_1 = succinimidomethyl, $R_2 = R_3$ = H).—A mixture of the above thiol (1·1 g.), paraformaldehyde (0·15 g.), and chloroform (15 ml.) was saturated with hydrogen chloride. After 1 day, the reaction mixture was poured into water and the chloroform distilled off. The *bisthio-methane* which separated from the aqueous layer was recrystallised from acetic acid and had m. p. 212—216° (Found: C, 60·3; H, 4·9; N, 6·4. $C_{23}H_{22}O_4N_2S_2$ requires C, 60·8; H, 4·8; N, 6·2%).

Bis-p-*succinimidomethylphenylsulphonylmethane* (IV; R_1 = succinimidomethyl, $R_2 = R_3$ = H).—(*a*) The above bisthio-methane (0·6 g.) was oxidised in glacial acetic acid (40 ml.), in which it is sparingly soluble, with 60% hydrogen peroxide (16 ml.) as described in preceding experiments. The *disulphone* was recrystallised from a large volume of acetic acid and obtained as a white powder, m. p. 295—298° (Found: C, 53·6; H, 4·6; N, 5·3. $C_{23}H_{22}O_8N_2S_2$ requires C, 53·3; H, 4·2; N, 5·4%).

(*b*) When the bisthio-methane (7 g.) was heated with 2N-sodium hydroxide (50 ml.), it dissolved with formation of the succinyl derivative. A 3% aqueous potassium permanganate solution (9 g. of permanganate) was then added with vigorous stirring while carbon dioxide was passed through the mixture. The whole was filtered, and the filtrate decolorised with sulphur dioxide and acidified, a precipitate separating which, recrystallised from acetic acid, melted at 188—190°. On refluxing of this substance with 2N-hydrochloric acid, the succinimido-derivative, m. p. 295—298°, identical with that prepared by method (*a*), was formed.

Hydrolysis of bis-*p*-succinylaminomethylphenylsulphonylmethane (1·3 g.), m. p. 188—190°, as obtained above, by refluxing with a solution of potassium hydroxide (4 g.) in water (20 ml.) for 4 hours yielded bis-*p*-aminomethylphenylsulphonylmethane, the constitution of which was established by acetylating it to give the previously described diacetyl derivative (IV; $R_1 = CH_2{\cdot}NHAc$, $R_2 = R_3 = H$), m. p. 236—239°.

RESEARCH DEPARTMENT, ROCHE PRODUCTS LTD.,
WELWYN GARDEN CITY, HERTS.

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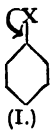
129. *A Connection between the Size of an Atom and the Magnitude of its Mesomeric and Electromeric Effects.*

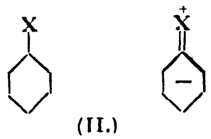
By G. BADDELEY.

The ability of a covalently bonded atom to donate electrons is shown to be a function of the direction of the electron displacement. Atoms with a covalent-bond radius which is small relative to the atomic radius are shown to be sterically the most suitable for participation in double-bond formation.

THE mesomeric electron release by halogen, which was first represented by a curved arrow as in (I) * and subsequently interpreted as a resonance hybrid of canonical structures as in (II) *, has been assumed to increase in the order F < Cl < Br < I (Ingold, *Rec. Trav. chim.*, 1929, **48**, 797). This order, which was later supported by the mesomeric moments of the halogenobenzenes (Sutton, *Proc. Roy. Soc.*, 1931, *A*, **133**, 668), was soon recognised to be inconsonant with the effect of nuclear attached halogen on the reactivities of aromatic side chains (Shoesmith and Slater, *J.*, 1926, 214; Ingold, *Ann. Reports*, 1927, 156). The chemical data were collated by Bennett and Baddeley (*J.*, 1933, 261; see also Bennett, *J.*, 1933, 1112) and led these authors to conclude that the mesomeric and electromeric release of electrons by halogen decreases in the order F > Cl > Br > I. Branch, Yabroff, and Bettmann (*J. Amer. Chem. Soc.*, 1934, **56**,



(I.)



(II.)

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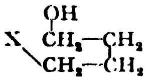
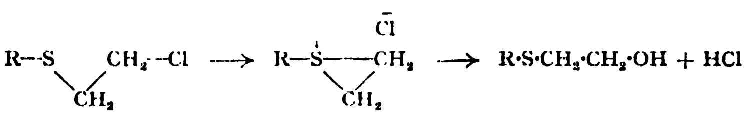
* In this paper double bonds are not shown in benzene rings.

1868) reached the same conclusion independently in the following year. This reversed order, which was subsequently confirmed by accurate determinations of mesomeric moments by Groves and Sugden (*J.*, 1937, 1992) and by Audsley and Goss (*J.*, 1942, 497), has been further substantiated by Bennett and others. Recently the data have been summarised and augmented by Baker and Hopkins (*J.*, 1949, 1089).

The original and very plausible assumption (Ingold, *loc. cit.*) that the mesomeric and electromeric release of electrons increases in the sequence $F < Cl < Br < I$ derived, at least indirectly, from the decrease in the ionisation potential in passing from the smaller to the larger halogen atoms. There is ample evidence, however, that the ability of an atom to participate in double-bond formation by releasing electrons in the direction of an atom to which it is already covalently attached is not directly related to its ability to release electrons in other directions. This is clearly illustrated by the following comparison of the contributions made by sulphur and oxygen respectively to the properties of some organic compounds containing one or both of these elements.

When a thioether RSR′ forms a sulphonium salt $RR'R''\overset{+}{S}\,\overset{-}{X}$, the direction of the release of electrons by the sulphur atom makes an angle of approximately 110° with the bonds joining this atom to R and R′ and occurs far more readily than the corresponding release of electrons by the oxygen atom of the ether ROR′. Bennett and Mosses (*J.*, 1931, 2956) suggested that the interaction of the δ-hydroxy-sulphide (III; X = SPh) with hydrobromic acid is greatly facilitated by the sulphur atom which " allows one of its lone pairs of electrons to take part in the process whereby the hydroxyl group becomes separated from the carbon atom to which it is attached." This type of activation is apparent, but in much smaller degree, for both the glycol (III; X = OH) and the phenoxy-alcohol (III; X = OPh) (Bennett and Reynolds, *J.*, 1935, 131).


(III.)

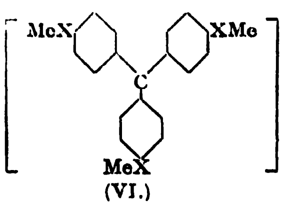

(IV.)

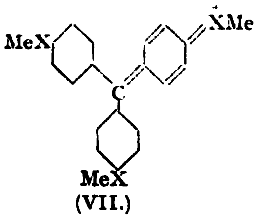
The ready unimolecular hydrolysis of 2-chloroethyl sulphides (IV) is a consequence of a release of electrons by sulphur to the 2-carbon atom (Bennett and Baddeley, *loc. cit.*; Baddeley, Thesis, Sheffield, 1932). This electron displacement makes an angle of approximately 60° with the bond joining the sulphur atom to the 1-carbon atom and is not apparent in the rates of hydrolysis of the corresponding 2-chloro-ethers (Böhme and Sell, *Ber.*, 1948, **81**, 123). Fehnel and Carmack (*J. Amer. Chem. Soc.*, 1949, **71**, 84) have shown that the optical interaction of a sulphur atom with a vinyl, carbonyl, or carbalkoxyl group is not destroyed when a methylene group is interposed; this release of electrons to a " β-carbon atom " becomes negligible in each instance when the sulphur atom is replaced by oxygen.

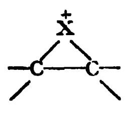
On the other hand, oxygen has a greater tendency than has sulphur to adopt the onium state by double-bond formation: $R'{-}X{-}R \longrightarrow R'{-}\overset{+}{X}{=}\overset{-}{R}$ (X = O or S). The very ready hydrolysis of α-chloro-ethers and -thio-ethers (V; X = O and S respectively) is probably due to an electron displacement of this type (Hughes and Ingold, *J.*, 1935, 248), and the chloro-ethers are the more reactive (Böhme, *Ber.*, 1941, **74**, 248; see also Leimu and Salomaa, *Acta Chem. Scandinavica*, 1947, **1**, 353).

$$\text{(V.)}\quad R{\cdot}X{\cdot}CH_2Cl \longrightarrow R{\cdot}\overset{+}{X}{=}CH_2\,\overset{-}{Cl} \longrightarrow \text{Products of hydrolysis}$$

The *pp′p″*-trimethoxytriphenylcarbonium ion (VI; X = O) is more stable than the *pp′p″*-trismethylthiotriphenylcarbonium ion (VI; X = S) (Brand, *J. pr. Chem.*, 1925, **109**, 36). Thus quinonoid structures of type (VII), in which electron release by X results in double-bond formation, make a greater contribution to the actual state of the ion when X = O than when X = S.


(VI.)


(VII.)


(VIII.)

This reversal is further illustrated by the data in the table below (Bennett and Hafez, *J.*, **1941**, 652). An *ortho*-substituent in 2-phenylethyl alcohol is suitably placed to donate electrons directly to the hydroxymethylene group, and the *o*-methylthio-group provides a much faster reaction with hydrobromic acid than does the *o*-methoxyl group. On the other hand, the methoxyl group is the more effective in the *p*-position; here the release of electrons is into the benzene ring and results in double bonding.

Velocities of reaction of substituted alcohols $C_6H_4X\cdot CH_2\cdot CH_2\cdot OH$ *with hydrobromic acid at* 80°: k × 10^4.

X =	NO_2.	H.	I.	SMe.	OMe.
p-	1·65	5·90	6·9	11·0	106
o-	3·10	5·90	3·25	6,840	35·0

Briefly, *the oxygen atom releases electrons more readily in the direction of its covalent bonds than does the sulphur atom, whereas the latter provides the readier release of electrons in other directions. This reversal is also observed among the halogens.*

The reactivities of *cyclo*hexanol derivatives towards hydrohalogen acids and the rates of acetolysis of *cyclo*hexyl *p*-bromobenzenesulphonates provide evidence of an electron release by *trans*-2-halogen and a readiness to form cylic intermediates of type (VIII; X = halogen) which decreases in the order I > Br > Cl (Winstein, Grunwald, *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 816, 821). On the other hand, the magnitude of the mesomeric effect of halogen when attached to a benzene ring is directly related to the ability of halogen to release electrons in the direction of the C_6H_5–halogen bond and, as mentioned at the outset, decreases in the order F > Cl > Br > I. Data given by Brockway (*J. Physical Chem.*, 1937, **41**, 747) for the carbon–halogen bond lengths in the halogenomethanes has led Pauling (" Nature of the Chemical Bond," Cornell, 1940, p. 236) to deduce " that chlorine has about one-half the power to form double bonds that fluorine has."

Although it is generally recognised that the ability to form double bonds decreases from the elements of the first row to those of the second and lower rows of the Periodic Table, no wholly satisfactory explanation has yet been found. The following simple consideration indicates that atoms with a covalent-bond radius which is small in comparison with the atomic radius are sterically the most suitable for double-bond formation. A double bond comprises a σ bond and a π bond, the latter resulting from the overlap of a *p*-orbital of one atom with a *p*-orbital of the other. These *p*-orbitals are directed perpendicularly to the σ bond and their ability to overlap one another must be directly related to the extent to which each atom contacts the flank of the other. Double bonding is therefore more likely between atoms which bite deeply into one another; that is, between atoms with a single-bond radius (r) which is small in comparison with the packing radius (R). Pauling (*op. cit.*, p. 192) has related these two radii by equation (i), whereas Rees (*J. Chem. Physics*, 1948, **16**, 995) prefers equation (ii). Rewritten as equations (iii) and (iv) respectively, they show that the quotient R/r decreases as the size of the atom increases.

(i) $R = r + 0{\cdot}8$ A. (iii) $R/r = 1 + 0{\cdot}8/(R - 0{\cdot}8)$

(ii) $R^2 = r^2 + 1{\cdot}22^2$ (iv) $R/r = [1 + 1{\cdot}22^2/(R^2 - 1{\cdot}22^2)]^{\frac{1}{2}}$

The quotient R/r for several elements is computed in the accompanying table. The necessary data have, with one exception, been extracted from Rees's paper, and parentheses indicate that R is obtained by substituting for r in equation (ii). The quotient decreases in the order F > Cl > Br > I and O > S, as does the ability of these atoms to form double bonds.

	Element.	*r*.	*R*.	*R/r*.		Element.	*r*.	*R*.	*R/r*.
1st Period	H	0·37	1·25	3·38	2nd Period	Cl	0·995	(1·56)	1·58
	F	0·64 *	(1·38)	2·15		S	1·04	(1·60)	1·54
	O	0·735	1·39	1·90		P	1·10	(1·64)	1·49
	N	0·73	(1·42)	1·94		Si	1·16	(1·68)	1·45
	C	0·77	(1·43)	1·87					
	B	0·89	(1·51)	1·70	3rd Period	Br	1·14	1·65	1·44
						Se	1·16	1·73	1·49
					4th Period	I	1·33	1·77	1·33
						Te	1·37	1·87	1·26

* Pauling, *op. cit.*, p. 179.

The contributions made by each of the canonical structures A–X and $\overset{-}{A}{=}\overset{+}{X}$ to the actual state of the molecule AX is determined by the difference in energy between these two structures.

The energy, Q, absorbed in passing from $A^{-}X$ to $\overset{-}{A}{=}\overset{+}{X}$ comprises three terms: $Q = I - E - D$, where I and E are respectively the ionisation potential of X and the electron affinity of A in $A^{-}X$, and D is the heat of dissociation of the π bond:

$$A{-}X \xrightarrow{I} A{-}\overset{+}{X} + e \xrightarrow{-E} \overset{-}{A}{-}\overset{+}{X} \xrightarrow{-D} \overset{-}{A}{=}\overset{+}{X}$$

When X represents the elements of one group of the Periodic Table, *e.g.*, the halogens, both I and D decrease in magnitude in passing from the smaller to the larger atoms, and the observed order F > Cl > Br > I for the mesomeric release of electrons indicates that D is more susceptible than is I to variation with change of element. On the other hand, atoms of elements in the same period of the Table have approximately the same size and the mesomeric release of electrons decreases, *e.g.*, N > O > F, as the ionisation potential increases.

The author expresses his indebtedness to Professor G. M. Bennett, C.B., F.R.S., for his valuable advice and criticism.

College of Technology, Manchester. [*Received, November 26th,* 1949.]

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130. *The Autoxidation of* iso*Propylbenzene.**

By G. P. Armstrong, R. H. Hall, and D. C. Quin.

A new technique has been used for the autoxidation of *iso*propylbenzene to give αα-dimethylbenzyl hydroperoxide. An alkaline (pH 8·5—10·5) oil-in-water emulsion of the hydrocarbon absorbs oxygen at 85° to give a good yield of the hydroperoxide identical with that previously reported by Hock and Lang (*Ber.*, 1944, 77, 257). The characteristics of the autoxidation are consistent with a radical-chain mechanism.

The autoxidation of *iso*propylbenzene to the hydroperoxide has been described by Hock and Lang (*Ber.*, 1944, **77**, 257), who oxidised the dry purified hydrocarbon at 85° while irradiating it with ultra-violet light.

$$C_6H_5{\cdot}CHMe_2 + O_2 \longrightarrow C_6H_5{\cdot}CMe_2{\cdot}O{\cdot}OH$$

The sodium salt of the hydroperoxide was precipitated from the product by treatment with 25% aqueous sodium hydroxide; the free hydroperoxide was liberated from the salt by careful treatment with the calculated amount of mineral acid, and further purified by distillation *in vacuo*. The overall yield of hydroperoxide was 90% based on the oxygen consumed, but the rate of oxidation was slow, only 0·2 g.-mol. of oxygen being absorbed by 3 g.-mols. of *iso*propylbenzene in 24 hours.

In 1945 when the present work was commenced, the only other reported work on the uncatalysed liquid-phase autoxidation of *iso*propylbenzene was that of Stephens (*J. Amer. Chem. Soc.*, 1926, **48**, 2920), who treated *iso*propylbenzene with oxygen in dim diffused light for 3—5 weeks at 80—104°, and obtained acetophenone and formic acid in low yields, as well as a little unidentified oil. He did not report the occurrence of peroxides in his products but observed that the presence of water favoured the oxidation slightly, whereas with toluene and ethylbenzene water inhibited oxidation.

After the work described below had been completed, the Hercules Powder Co. (U.S.P. 2,438,125) described the autoxidation of *iso*propylbenzene with air or oxygen at low temperatures in the presence of dilute alkali and activated carbon. The products contained peroxides which were not isolated but were subsequently destroyed by hot sodium hydroxide solution.

Several reports describe the metal-catalysed autoxidation of *iso*propylbenzene, the earliest being D.R.P. 522,255 (I.G. Farbenind. A.-G.; *Zentr.*, 1931, I, 3721). Acetophenone and phenyldimethylcarbinol were identified among the products. Similar results were obtained by the Monsanto Chemical Co. (U.S.P. 2,447,400) who used oxygen in the presence of calcium hydroxide.

We found the rate of absorption of oxygen by an alkaline oil-in-water emulsion of *iso*propylbenzene at 85° to be much more rapid than that reported by Hock and Lang (*loc. cit.*), and obtained considerably higher concentrations of hydroperoxide in the products. The hydroperoxide was isolated from the oxidised hydrocarbon layer by fractional distillation *in vacuo*, or by precipitation of the hydrated sodium salt with 25% w/w sodium hydroxide solution and subsequent regeneration of the free hydroperoxide with carbon dioxide. Contrary to the implied observation of Hock and Lang precipitation of the sodium salt with a slight excess of sodium hydroxide was only about 50% complete, several treatments with fresh batches of alkali being necessary to complete the precipitation. Similarly several extractions with an excess of dilute (8%) sodium hydroxide were necessary for complete extraction of the hydroperoxide into aqueous solution. This behaviour is typical of a very weak acid.

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* This paper is covered by B.P. 610,293 and pending applications.

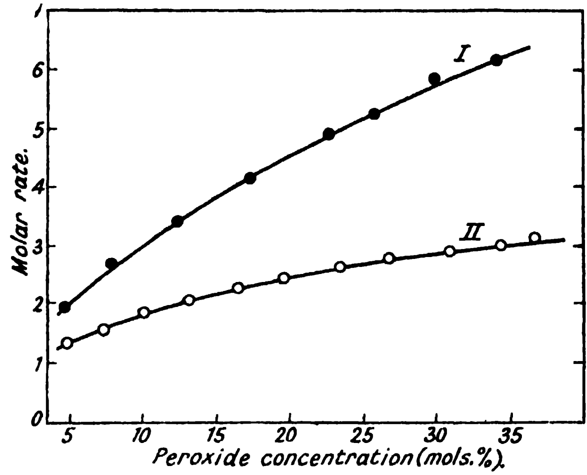
The structure of the hydroperoxide was confirmed by decomposition of the pure hydroperoxide with aqueous (10% w/v) sulphuric acid under reflux to give phenol (70—80%) and

$$C_6H_5{\cdot}CMe_2{\cdot}O{\cdot}OH \longrightarrow C_6H_5{\cdot}OH + Me_2CO$$

acetone (70%) (cf. Hock and Lang, *loc. cit.*). Small amounts of acetophenone and α-methylstyrene were obtained as by-products. It is of interest that this decomposition can be carried out equally well with the hydroperoxide in the untreated oxidation product.

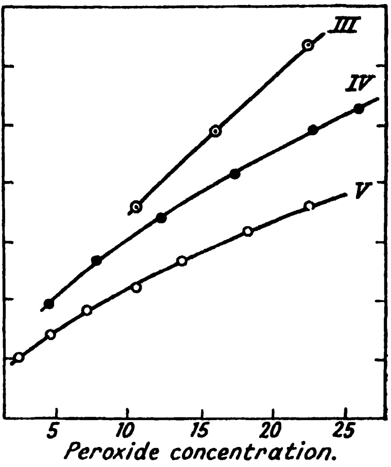
Reduction of the hydroperoxide with aqueous sodium hydrogen sulphite gave phenyldimethylcarbinol, some α-methylstyrene being formed by dehydration of the carbinol; and traces of acetophenone were again obtained.

FIG. 1.



I. 0·3% *Sodium stearate.* II. 0·4% *Teepol.*

FIG. 2.



III. *Phase ratio* 5 : 1. IV. *Phase ratio* 2 : 1. V. *Phase ratio* 1 : 1.

Preliminary work on the oxidation indicated that acids were produced in small quantities which lowered the pH of the emulsion sufficiently to slow down the oxidation. The initial presence of sodium carbonate (1·3% of the aqueous phase) provided a sufficient reserve of alkalinity without producing too high a pH in the initial stages. The presence, in the *iso*propylbenzene, of styrene and α-methylstyrene also retarded the oxidation and increased the rate of acid formation. Satisfactory starting material was obtained by hydrogenation of the crude hydrocarbon and careful fractionation of the product.

Under neutral (pH 7·4) or acid (pH 4·7) conditions, or at alkaline pH in the absence of emulsifying agent, the rate of oxidation was slow, being of the same order as the rate in the homogeneous phase at the same temperature. At high alkalinity (5—10% NaOH), the reaction efficiency (based on oxygen absorbed and hydroperoxide produced) was low, being of the order of 50%. The optimum conditions of alkalinity for a high efficiency at a reasonable rate were pH 8·5—10·5, conveniently achieved by the addition of sodium carbonate.

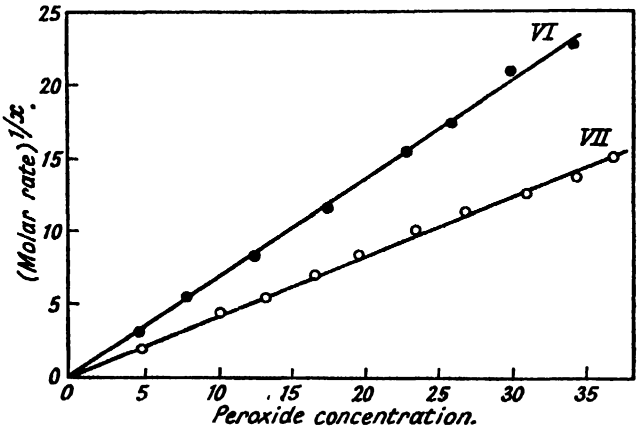
Two emulsifying agents were tried, sodium stearate and " Teepol " (an aqueous solution of mixed sodium higher-alkyl sulphates). Variation of the sodium stearate concentration between 0·09 and 0·35% w/v or of that of " Teepol " between 0·2 and 2·5% v/v in the aqueous phase did not significantly change the respective oxidation rates. However, the rate at any given hydroperoxide concentration was higher in the case of sodium stearate (Fig. 1).

The molar rate of oxidation, expressed as mols. of oxygen absorbed per hour per 100 mols. of *iso*propylbenzene present, increased with increasing water : oil phase ratio (Fig. 2), although the oxygen absorption rate per unit volume of total liquid decreased.

In the early stages of the reaction the yield of hydroperoxide based on oxygen absorbed was almost quantitative, but at 20% hydroperoxide concentration it had fallen to about 90%. The reaction was very sensitive to traces of metallic impurities, the addition of copper or lead, even as the metals, producing an immediate effect; a sharp initial rise in the rate of oxidation was followed by a rapid decline to a low value. The oxidation efficiency also fell rapidly, and the products contained up to 1 part of acetophenone for every 2 parts of hydroperoxide.

The oxidations followed a course analogous to other free-radical-chain autoxidations, for example, those of tetralin (Robertson and Waters, *Trans. Faraday Soc.*, 1946, **42**, 201) and ethyl linoleate (Bolland, *Proc. Roy. Soc.*, *B*, 1946, **186**, 218). In the absence of added catalysts an induction period of about 1·5 hours, during which the oxygen absorption was almost imperceptible, was followed by an autocatalytic reaction. Subsequently the oxidation rate passed through a maximum value. The induction period could be eliminated by the addition of organic peroxides (benzoyl, lauryl) or of the hydroperoxide itself. Phenol inhibited the oxidation, and styrene and α-methylstyrene exerted a retarding influence (see above).

FIG. 3.



	k.	*x*.
VI. 0·3% *Sodium stearate*	0·80	0·58
VII. 0·4% *Teepol*	0·69	0·42

The molar rate of oxygen absorption in the autocatalytic reaction depended on the hydroperoxide concentration according to the relation

$$\text{Molar rate} = \frac{-d[O_2]/dt}{[RH]} = k[RO{\cdot}OH]^x$$

For a unimolecular rate of hydroperoxide decomposition the value of x expected on theoretical grounds would be 0·5 (Bolland and Gee, *Trans. Faraday Soc.*, 1946, **42**, 241). The values found approximated to this figure (Fig. 3), but with some variation. In particular the use of " Teepol " as emulsifying agent led to values of x below 0·5. A full investigation of the kinetics of the autoxidation of *iso*propylbenzene in both emulsion and single phase has been made (Twigg *et al.*, unpublished work).

The relation given above was valid up to a certain hydroperoxide concentration, which varied from one experiment to another, the highest found being 34 molar-%. Soon after this the rate passed through its maximum value. The hydroperoxide concentration continued to increase after the maximum rate had been passed, and in some cases also passed through a maximum. Where the maximum rate was observed at 34 molar-% of hydroperoxide, the concentration of the latter increased to 47 molar-% without having reached a maximum value. In other cases maximum values of both rate and hydroperoxide concentration were reached at lower extents of oxidation.

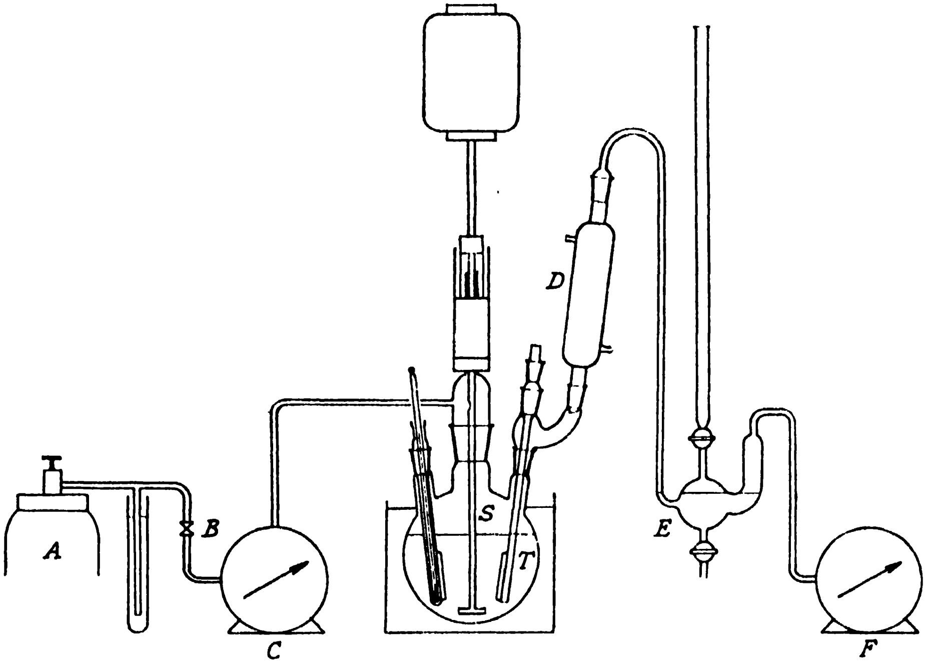
EXPERIMENTAL.

M. p.s and b. p.s are uncorrected.

Oxidation Apparatus (Fig. 4).—The oxygen feed from the supply cylinder *A* was controlled by a valve *B* operating at constant up-stream pressure, and passed *via* a ½-l. wet gasmeter *C* to the vapour space above the liquid in the reaction vessel (a 1-l. Pyrex flask). The gas in the reaction vessel was circulated continuously through the liquid by a recycle stirrer *S*, before passing *via* the reflux condenser *D* and a bubbler *E* to a second gasmeter *F*. The bubbler contained aqueous phenolphthalein and was fitted with a burette for the addition of 0·2N-sodium hydroxide, as a rough indication of the carbon dioxide evolved. The reaction vessel was immersed in a thermostatically controlled bath, and was fitted with a thermometer pocket and a liquid-sampling tube *T*, to which were sealed glass strips to act as baffles and prevent swirling of the liquid. The seal on the stirrer shaft was filled with mercury or liquid paraffin.

Materials.—Oxygen was obtained in about 98% purity from standard commercial cylinders. *iso*Propylbenzene was received as a commercial grade containing 1—5% of styrene + α-methylstyrene. The crude material was hydrogenated for 2 hours at 60—80° and atmospheric pressure with 5% of Raney nickel as catalyst, and the hydrogenated product fractionated to give, as main fraction, *iso*propylbenzene, b. p. 153·5—154°/753 mm., n_D^{20} 1·4911, containing less than 0·005% of styrene (by ultra-violet absorption). The other materials used were of " AnalaR " grade, or in the case of sodium stearate the purest obtainable (British Drug Houses, Ltd.; made from purified stearin). " Teepol " was the commercial product supplied by Shell Chemicals Ltd.

FIG. 4.



Analytical.—*iso*Propylbenzene was examined for styrenes by ultra-violet absorption by Mr. A. R. Philpotts of this Department, whom we thank. The oxidation products were analysed for hydroperoxide as follows: Samples (1 ml.) of emulsion were pipetted into 250-ml. conical flasks each containing 25 ml. of freshly redistilled glacial acetic acid. The air in each flask was displaced by nitrogen (from cylinders; " oxygen-free " grade), and 1 ml. of saturated aqueous potassium iodide added. The flasks were stoppered and set aside for 15 minutes at room temperature, after which the liberated iodine was titrated with 0·05N-thiosulphate. Blank determinations on the acetic acid required about 0·1 ml. of 0·05N-thiosulphate.

Oxidation Procedure.—The thermostat was brought to the required temperature (normally 85°), and the air in the reaction vessel replaced by oxygen. The alkaline aqueous phase containing the emulsifying agent was introduced and allowed to reach the bath temperature. *iso*Propylbenzene was then added and the stirrer and gas circulation were started. Samples were withdrawn periodically for hydroperoxide analysis, and regular readings taken of the gasmeters.

Recovery of the Hydroperoxide.—The oxidation product was cooled to room temperature, saturated with carbon dioxide, the oil layer separated, and its hydroperoxide content determined. Subsequent treatment of the oil layer was by one of the following methods:

(*a*) The oil was cooled below room temperature, stirred, and treated dropwise with a slight excess (calculated on the oxygen absorption) of cold 25% w/w aqueous sodium hydroxide. The white crystals which separated were collected, washed with light petroleum (b. p. 40—60°), and dried in a vacuum. The *iso*propylbenzene mother-liquors still contained hydroperoxide, most of which was recovered as sodium salt by successive treatments with strong alkali as outlined above.

The sodium salt was converted into free hydroperoxide, if desired, as follows. A suspension of the salt in water was covered with light petroleum and saturated with carbon dioxide. The upper layer was separated, washed with a little water, dried (Na_2SO_4), and evaporated *in vacuo*. Distillation of the residual free hydroperoxide at low pressure gave a colourless oil, b. p. 53°/0·0005 mm. (pump pressure), n_D^{20} 1·5242, d_4^{20} 1·062 (Found: C, 71·4; H, 8·05; active O, 10·5. Calc. for $C_9H_{12}O_2$: C, 71·05; H, 7·95; active O, 10·5%) (Hock and Lang, *loc. cit.*, give b. p. 53°/0·1 mm., 60°/0·2 mm., n_D^{20} 1·52424, d_4^{20} 1·06189). M_D^{20} was 43·86 (Calc. for *iso*propylbenzene: 40·16); the increment for the –O–O– group was thus 3·70.

(*b*) The oil was distilled *in vacuo*. The unchanged *iso*propylbenzene was recovered first, at 41—46°/13 mm. It contained traces of α-methylstyrene (identified by its ultra-violet absorption) and acetophenone (identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic specimen 242—244°). When all the low-boiling material had been removed, a residue of hydroperoxide remained which was distilled *in vacuo*.

Acid Decomposition of the Hydroperoxide (cf. Hock and Lang, *loc. cit.*).—(*a*) A mixture of the sodium salt (2 g.) of the hydroperoxide and 10% w/w sulphuric acid (25 c.c.) was refluxed for 1¼ hours, the top of the reflux condenser being connected to a tube dipping into ice-cold water. A very slow current of water at 50—60° was passed through the condenser. When the heating was stopped the liquid in the trap connected to the top of the condenser was treated with a solution of 2 : 4-dinitrophenylhydrazine in 5N-hydrochloric acid. The yellow flocculent precipitate which separated, was recrystallised from 95% ethanol; it formed yellow needles, m. p. 126—127°, undepressed on admixture with authentic acetone 2 : 4-dinitrophenylhydrazone.

The acid hydrolysate obtained was treated with sodium hydroxide pellets (3·5 g.) and filtered, and the filtrate benzoylated at 0° with benzoyl chloride. The solid which separated was recrystallised from 95% ethanol, whereafter it had m. p. 67°, undepressed on admixture with authentic phenyl benzoate.

In a subsequent similar experiment the hydrolysate was steam-distilled, the distillate acidified and treated with excess of bromine water, then with excess of potassium iodide solution, and finally with sodium thiosulphate solution to remove free iodine. 2 : 4 : 6-Tribromophenol, m. p. 93—94°, was obtained (lit., 92° to 96°).

(*b*) A mixture of the sodium salt (50 g.) of *iso*propylbenzene hydroperoxide (equivalent to 25·5 g. of free hydroperoxide) and dilute sulphuric acid (560 c.c. of water and 35 c.c. of concentrated sulphuric acid) was steam-distilled until free from phenol (bromine water test on the distillate). The main bulk of distillate, which contained some water-insoluble oil, was treated with excess of sodium hydroxide solution, and the aqueous layer was separated. The remaining oil was washed with dilute sodium hydroxide solution and then with water, dried (Na_2SO_4), and filtered. A colourless oil (4·5 c.c.) was obtained. A portion gave acetophenone 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p.). The main bulk of the oil was distilled at atmospheric pressure, the following fractions being obtained: (i) b. p. 160—165° (0·9 c.c.), n_D^{20} 1·5370, (ii) b. p. 165—210° (2·8 c.c.), n_D^{20} 1·5325, and (iii) b. p. 240—250° (0·5 c.c.), n_D^{20} 1·5467.

Fraction (i) was α-methylstyrene (lit., b. p. 162—164°, n_D^{20} 1·5384), its identity being confirmed by its ultra-violet absorption. Fraction (ii) was refractionated, more α-methylstyrene being obtained (2·1 c.c.; b. p. 160—173°). The high-boiling material was not identified.

(*c*) A mixture of sulphuric acid (17 c.c. of concentrated sulphuric acid and 270 c.c. of water) and a solution (175 c.c.) of *iso*propylbenzene hydroperoxide (65·6 g.) in *iso*propylbenzene was stirred vigorously and refluxed for 90 minutes. Steam-distillation of the mixture yielded a distillate consisting of two layers. The acetone content of the aqueous layer was determined by oximation, and the phenol content by the bromide–bromate method.

The acetone content of the oil layer was determined by repeated washing of an aliquot with water and determination of acetone in the washings. The phenol content of the layer was determined by extracting an aliquot with a large excess of N-sodium hydroxide and determining the phenol content of the alkaline extract. The total yields of phenol and acetone were 82% and 74%, respectively, based on the initial weight of *iso*propylbenzene hydroperoxide.

Reduction of the Hydroperoxide with Sodium Hydrogen Sulphite.—The hydrated sodium salt (830 g.) of the hydroperoxide (equiv. to *ca.* 410 g. of free hydroperoxide) was added gradually to a vigorously stirred aqueous solution (2·4 l.) of sodium hydrogen sulphite (480 g.) which was kept at <20°, the resultant mixture stirred for a further 45 minutes at room temperature, and the oil extracted with ether. The ethereal solution was washed with dilute sodium hydroxide solution and then with water, and dried (Na_2SO_4), and the ether distilled off, to yield an oil (295 g.) which was fractionated *in vacuo* through a 30 × 1·5-cm. helices-packed, jacketed, glass column. α-Methylstyrene (38 g.) was collected, mainly at 51·5—52·5°/12 mm., and, after a small intermediate fraction, phenyldimethylcarbinol (246 g.) distilled at 90—92°/11 mm. This material (n_D^{20} 1·5210) contained traces of acetophenone from which it cannot readily be separated by distillation (cf. Klages, *Ber.*, 1902, **35**, 2637). When kept, it yielded large, transparent, colourless crystals, m. p. 25—27°, which on recrystallisation from light petroleum (b. p. 40—60°), cooled in ethanol–solid carbon dioxide, yielded small white crystals, m. p. 34—35° (Matsubara and Perkin, *J.*, 1905, 671, give m. p. *ca.* 35—37°). The carbinol on dehydration with boiling acetic anhydride (Staudinger and Breusch, *Ber.*, 1929, **62**, 449) gave α-methylstyrene, b. p. 50—50·5°/11 mm., n_D^{20} 1·5384, in good yield.

The authors are indebted to the Directors of the Distillers Company, Ltd., for permission to publish this paper. The microanalysis was by Drs. Weiler and Strauss of Oxford.

THE DISTILLERS COMPANY LIMITED,
RESEARCH AND DEVELOPMENT DEPARTMENT,
EPSOM, SURREY.

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131. *Deoxy-sugars. Part IX. Some Properties and Reactions of 2-Deoxy-D-galactose.*

By W. G. OVEREND, F. SHAFIZADEH, and M. STACEY.

2-Deoxy-D-galactose, conveniently synthesised by the glycal method, gives an interesting series of highly crystalline derivatives. The reactions and general properties of the oxidation product are closely similar to those described for other 2-deoxy-hexoses and -pentoses. The synthesis and determination of the structure of the methyl-glycopyranosides and -glycofuranosides of 2-deoxy-D-galactose are described.

WE have extended our studies of deoxy-sugars, and in particular of 2-deoxy-pentoses and -hexoses to include 2-deoxy-D-galactose; the preparation of this compound was reported by Isbell and Pigman (*J. Res. Nat. Bur. Stand.*, 1939, **22**, 397) but not its derivatives or reactions. We found that 2-deoxy-D-galactose could be synthesised in satisfactory yield from D-galactose by the improved glycal method. We noted that the Zemplén method for the deacetylation of 3 : 4 : 6-triacetyl D-galactal gave a better yield than that employing barium hydroxide as the deacetylating agent. Treatment of D-galactal with 5% sulphuric acid gave 2-deoxy-D-galactose. We observed that catalytic reduction of 3 : 4 : 6-triacetyl D-galactal yielded 3 : 4 : 6-*triacetyl* 1 : 2-*dideoxy-*D*-galactose,* deacetylation of which, using sodium in methanol, afforded 1 : 2-*dideoxy-*D*-galactose,* which was also obtained by catalytic reduction of D-galactal. Further investigations of these interesting dideoxy-sugars will form the subject of a later communication.

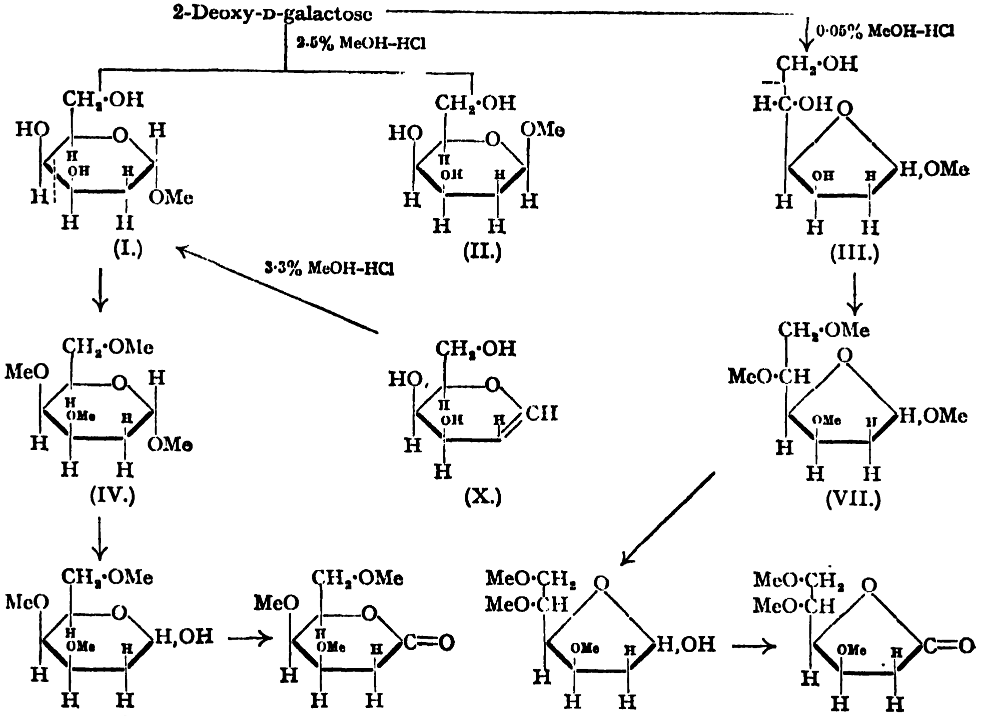
2-Deoxy-D-galactose exhibited mutarotation in water and in methanol. It formed a crystalline 2 : 4-*dinitrophenylhydrazone* and when treated with *p*-toluidine in ethanol gave 2-*deoxy-*D*-galactose* p-*toluidide.* Both derivatives are particularly useful for characterising the sugar. On acetylation with acetic anhydride in pyridine, 2-deoxy-D-galactose was converted into 1 : 3 : 4 : 6-*tetra-acetyl* 2-*deoxy-*α*-*D*-galactose,* whereas when fused sodium acetate and acetic anhydride were used as acetylating agents the β-isomer of the *tetra-acetate* was obtained. It was shown that 2-deoxy-D-galactose could react in its *aldehydo*-form, since when treated with ethanethiol and concentrated hydrochloric acid it gave crystalline 2-*deoxy-*D*-galactose diethyl mercaptal.* Oxidation of the deoxy-sugar with bromine in water was easily effected, the product being 2-*deoxy-*D*-galactonolactone.* Treatment of this lactone with liquid ammonia gave the corresponding *amide* which on being heated evolved ammonia. 2-Deoxy-D-galactonolactone was extremely stable and underwent no apparent hydrolysis in aqueous solution in 3 days, indicating that it was probably a furanolactone.

Methyl glyco-pyranosides of	Isomer.	M. p.	$[\alpha]_D$.	$[M]$.	$[M]_\alpha - [M]_\beta$.	Ref.
L-Arabinose	α	131°	+ 17·3°	2,840	−37,420	*a*
	β	169	+245·5	40,260		
2-Deoxy-L-ribose	α	99—100	− 43·4	− 6,420	−36,360	*b*
	β	83—84	+202·3	29,940		
D-Glucose	α	168	+158·9	30,830	+37,030	*c, d*
	β	110	− 31·97	− 6,200		
2-Deoxy-D-glucose	α	91—92	+138	+24,600	+33,180	*e, f*
	β	122—123	− 48·2	− 8,500		
D-Galactose	α	111	+178·8	33,300	+33,380	*g, h*
	β	178	− 0·42	−80·5		
2-Deoxy-D-galactose ...	α	112—113	+170	+30,300	+30,300	
	β	Syrup	± 0	0		

a, Hudson, *J. Amer. Chem. Soc.*, 1925, **47**, 270. *b*, Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836. *c*, Rüber, *Ber.*, 1924, **57**, 1797. *d*, Patterson and Robertson, *J.*, 1929, 300. *e*, Bergmann *et al.*, *Ber.*, 1922, **55**, 158. *f*, *Idem*, *ibid.*, 1920, **53**, 545. *g*, Fischer and Beensch, *ibid.*, 1894, **27**, 2480; 1895, **28**, 1145; Voss, *Annalen*, 1931, **485**, 283; Micheel and Littman, *ibid.*, 1928, **466**, 115. *h*, Müller, *Ber.*, 1931, **64**, 1820.

When 2-deoxy-D-galactose was treated with 2·5% methanolic hydrogen chloride for three hours it yielded a syrup from which was isolated a crystalline methyl-2-deoxygalactoside. This, as is subsequently described, was identified as α-methyl-2-deoxy-D-galactopyranoside (I) which was conveniently characterised by conversion into its 3 : 4 : 6-*tritoluene*-p-*sulphonyl* derivative. In addition to (I) a syrupy glycoside was obtained which in all probability consisted mainly of β-*methyl-2-deoxy-*D*-galactopyranoside* (II). Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1630) described the isolation of similar compounds but did not investigate their structures. Polarimetric observations on the specific rotations, in methanol, of the two glycosides served to differentiate between the α- and β-isomers in accordance with the well-known convention, first introduced by Hudson (*J. Amer. Chem. Soc.*, **1909**, 31, 66) (cf. Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836). Moreover the αβ-relation of the two isomeric glycosides was further confirmed by the observations which were made (polarimetrically) that 2% methanolic hydrogen chloride converts each glycoside into an αβ-mixture similar to that from which they were initially isolated (Fig. 1). Finally the αβ-relation between the two glycosides is evident from a consideration of the difference in molecular rotations. The molecular rotations of the α- and β-forms ($[M]_\alpha$ and $[M]_\beta$ respectively) of the methylglycopyranosides of L-arabinose, 2-deoxy-L-ribose, D-glucose, 2-deoxy-D-glucose, D-galactose, and 2-deoxy-D-galactose are compared in the annexed table (cf. Deriaz *et al.*, *loc. cit.*). There is good agreement between the difference in the molecular rotations of the respective α- and β-forms of methyl-2-deoxy-D-galactopyranoside and of methyl-D-galactoside.

When 2-deoxy-D-galactose was treated with 0·05% methanolic hydrogen chloride for a very short period, another methyl-2-deoxy-D-galactoside (III) was formed. This has been shown to be *αβ-methyl-2-deoxy-*D-*galactofuranoside* (cf. Deriaz *et al.*, *loc. cit.*, and Hughes, Overend, and Stacey, *J.*, 1949, 2846, for analogous results with 2-deoxy-D-ribose and 2-deoxy-D-glucose respectively).



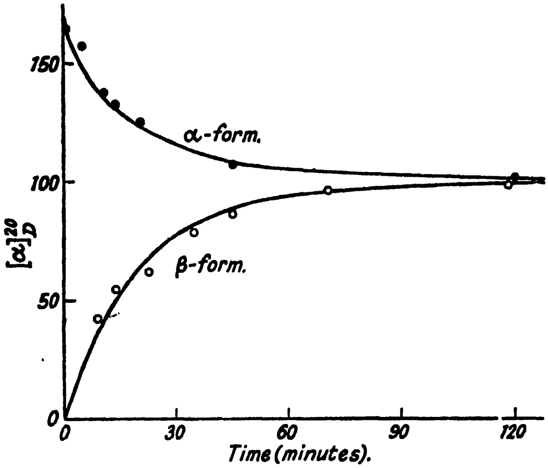
The following observed facts have led to the glycosides (I) and (III) being assigned the structures described.

(*a*) The glycoside (III) was much more rapidly hydrolysed with hydrochloric acid than glycoside (I). In Fig. 2 the rates of hydrolysis of the glycosides (I) and (III) and of αβ-methyl-D-galacto-pyranoside and -furanoside are compared. It is a general property of methylglycofuranosides to have a greater lability to acids than the corresponding pyranosides and this effect is enhanced in the series of 2-deoxy-sugars (Overend, Stacey, and Staněk, *J.*, 1949, 2841). This result indicates that the glycosides (I) and (III) are of the pyranose and furanose type respectively.

(*b*) When D-galactal (X) was treated with 3·3% methanolic hydrogen chloride it yielded the crystalline glycoside (I) (33%). Since D-galactal is known to have the pyranose structure (Levene and Tipson, *J. Biol. Chem.*, 1931, 93, 631) it is likely that (I) also has a pyranose structure (cf. Fischer, Bergmann, and Schotte, *Ber.*, 1920, 53, 509, for a similar approach in the glucose series).

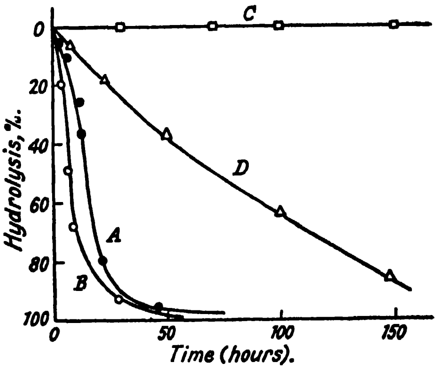
(*c*) It is well established (Hockett and McClenahan, *J. Amer. Chem. Soc.*, **1939**, **61**, 1667) that adjacent hydroxyl groups are readily oxidised by lead tetra-acetate and that *cis*- are more rapidly oxidised than *trans*-hydroxyl groups. Oxidation of the glycosides (I) and (III) with lead tetra-acetate resulted in both cases in the uptake of 1 mole of oxidant. The rate of oxidation was slightly faster for (I) than for (III) (see Fig. 3). Similarly adjacent hydroxyl groups may be oxidised by sodium metaperiodate (Jackson and Hudson, *J. Amer. Chem. Soc.*, **1939**, **61**, 1530).

FIG. 1.



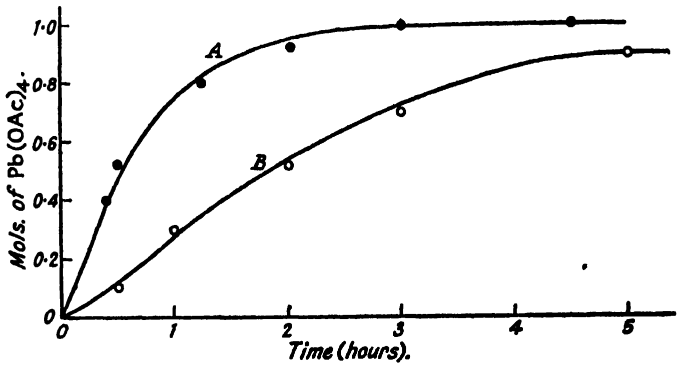
Isomerisation of α- *and* β-*methyl-2-deoxy-*D-*galactopyranoside by* 2·5% HCl *in* MeOH.

FIG. 2.



A. αβ-*Methyl-2-deoxy-*D-*galactofuranoside* (0·02N-HCl).
B. α-*Methyl-2-deoxy-*D-*galactopyranoside* (N-HCl).
C. αβ-*Methyl-*D-*galactopyranoside* (0·5N-HCl).
D. αβ-*Methyl-*D-*galactofuranoside* (N-HCl).

FIG. 3.
Oxidation by lead tetra-acetate.



A. α-*Methyl-2-deoxy-*D-*galactopyranoside.*
B. αβ-*Methyl-2-deoxy-*D-*galactofuranoside.*

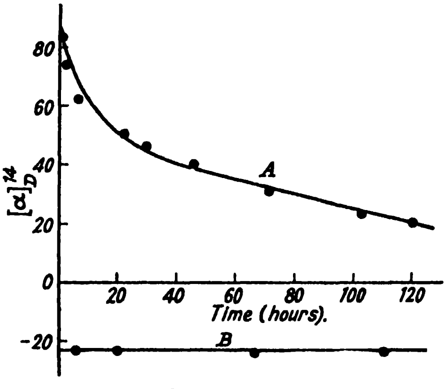
If one of the hydroxyl groups is primary then formaldehyde is formed. Both glycosides absorbed 1 mole of sodium metaperiodate, but formaldehyde resulted only from (III), thereby indicating that this glycoside was methyl-2-deoxy-D-galactofuranoside. The formaldehyde was determined as its dimedon derivative (Reeves, *J. Amer. Chem. Soc.*, **1941**, **63**, 1476).

(*d*) Finally, conclusive proof of the structures of the glycosides was obtained by the classical methods of carbohydrate chemistry, involving methylation of the glycoside, hydrolysis of the fully methylated derivative, oxidation of the products to methylated lactones, study of the rates of hydrolysis of the methylated lactones in water, etc. (Carter, Robinson, and Haworth, *J.*, 1930, 2125).

Thus α-methyl-2-deoxy-D-galactopyranoside (I) was methylated by the liquid ammonia technique (Muskat, *J. Amer. Chem. Soc.*, 1934, **56**, 693, 2449; Freudenberg and Boppel, *Ber.*, 1938, **71**, 2505). Smooth methylation occurred and 3 : 4 : 6-*trimethyl α-methyl-2-deoxy-*D-*galactopyranoside* (IV) was obtained as a colourless liquid. On treatment with N-hydrochloric acid at 70° it gave 3 : 4 : 6-*trimethyl* 2-*deoxy*-D-*galactopyranose* (V) as a colourless syrup. Oxidation of this with bromine in water afforded 3 : 4 : 6-*trimethyl* 2-*deoxy*-D-*galactonolactone* (VI). A similar series of reactions was carried out on αβ-methyl-2-deoxy-D-galactofuranoside (III). This was methylated in liquid ammonia with sodium and methyl iodide and 3 : 5 : 6-*trimethyl αβ-methyl-*2-*deoxy*-D-*galactofuranoside* (VII) was isolated. Hydrolysis of the glycosidic group by 0·01N-hydrochloric acid at 100° (20 minutes) gave 3 : 5 : 6-*trimethyl* 2-*deoxy*-D-*galactofuranose* (VIII) as a colourless syrup, whence oxidation in the normal way with bromine water gave 3 : 5 : 6-*trimethyl* 2-*deoxy*-D-*galactonolactone* (IX). The rate of hydrolysis of each of the lactones obtained was measured polarimetrically at room temperature. Hydrolysis of 3 : 4 : 6-trimethyl 2-deoxy-D-galactonolactone (VI) was complete in approximately 100 hours, whereas 3 : 5 : 6-trimethyl 2-deoxy-D-galactonolactone (IX) was hydrolysed exceedingly slowly (see Fig. 4), thereby showing that the original methylglycosides from which they were derived must have had the pyranose (I) and the furanose structure (III) respectively.

FIG. 4.

Hydrolysis of the lactones.



A. 3 : 4 : 6-*Trimethyl* 2-*deoxy*-D-*galactonolactone* (δ-*type*).
B. 3 : 5 : 6-*Trimethyl* 2-*deoxy*-D-*galactonolactone* (γ-*type*).

Thus it was apparent that the above reactions of 2-deoxy-D-galactose are closely analogous to those of 2-deoxy-D-ribose and 2-deoxy-D-glucose, and it seems that these will be typical for most 2-deoxy-hexoses and -pentoses.

EXPERIMENTAL.

3 : 4 : 6-*Triacetyl* D-*Galactal*.—Dry powdered 1-bromo 2 : 3 : 4 : 6-tetra-acetyl D-galactose (110 g.) was suspended in 50% acetic acid (1·6 l.), and the suspension was rapidly stirred. Zinc dust (300 g.) was slowly added during 2 hours. At intervals throughout the addition of the zinc a few drops of a 3% solution of platinic chloride were added. Stirring was continued for 3 hours and then the zinc was filtered off, and the filtrate concentrated to 500 c.c. and then poured into water (1 l.). The solution was extracted with chloroform (4 × 250 c.c.), and the extract washed first with aqueous sodium hydrogen carbonate and then with water. After being dried ($MgSO_4$) the solvent was evaporated and the syrupy residue distilled. Two fractions were obtained, (i) 48 g. (69%), b. p. 145—150° (bath temp.)/0·001 mm., n_D^{18} 1·4677, m. p. *ca.* 30°, $[\alpha]_D^{18}$ ±0° (*c*, 1·0 in ethanol) {this was triacetyl D-galactal (cf. Levene and Tipson, *J. Biol. Chem.*, 1931, **93**, 631, who give m. p. 30° and $[\alpha]_D^{20}$ −12·4° in chloroform, and Komada, *Bull. Jap. Chem. Soc.*, 1932, **7**, 211, who gives b. p. 138—140°/0·2—0·3 mm; Pigman and Isbell, *J. Res. Nat. Bur. Stand*, 1937, **19**, 204, who record b. p. 140—155°/0·005 mm.)}, and (ii) 1·1 g., b. p. 180—210° (bath temp.)/0·001 mm. (Found : C, 50·9; H, 6·3%). Trituration of (ii) with ethanol induced a portion to crystallise. This was separated and shown to be penta-acetyl D-galactose, m. p. 142° alone or on admixture with an authentic specimen. In addition some polymeric material remained undistilled. If the addition of platinic chloride solution was omitted the yield of triacetyl D-galactal was much reduced (*ca.* 30%) and much more penta-acetyl D-galactose was obtained.

3 : 4 : 6-*Triacetyl* 1 : 2-*Dideoxy*-D-*galactose*.—3 : 4 : 6-Triacetyl D-galactal (0·5 g.) was dissolved in dry methanol (50 c.c.) and hydrogenated at room temperature with a platinum oxide catalyst. The solution was filtered and evaporated to dryness. The syrupy residue was distilled and 3 : 4 : 6-*triacetyl* 1 : 2-*dideoxy*-D-*galactose* (0·45 g.) obtained as a colourless syrup, b. p. 120—130° (bath temp.)/1 mm., n_D^{21} 1·4558, $[\alpha]_D^{20}$ +55·9° (*c*, 0·32 in chloroform) (Found : C, 52·5; H, 6·8. $C_{12}H_{18}O_7$ requires C, 52·5; H, 6·6%).

D-*Galactal*.—(*a*) 3 : 4 : 6-Triacetyl D-galactal (32 g.) was added to a solution of barium hydroxide (90 g.) in water (450 c.c.). The solution was kept overnight at 0° and then heated for 30 minutes at 80°. Carbon dioxide was passed through the solution after cooling and the precipitated barium carbonate filtered off. The filtrate was evaporated at 55° to half its volume and then refiltered through a charcoal pad. Further evaporation gave crystals which were recrystallised from ethyl acetate. D-Galactal (10 g., 59%) had m. p. 104° and $[\alpha]_D^{18}$ +5° (*c*, 1·2 in methanol) (cf. Levene and Tipson, *loc. cit.*, and Komada *loc. cit.*, who give m. p. 100°, and Tamm and Reichstein, *Helv. Chim. Acta*, 1948, **31**, 1630, who give m. p. 90—92°).

(*b*) 3 : 4 : 6-Triacetyl D-galactal (87 g.) was dissolved in absolute methanol (1 l.), and sodium (0·2 g.) was added. The solution was kept for 48 hours and then solid carbon dioxide was added. The solution was evaporated to dryness, the residue was recrystallised from ethyl acetate, and D-galactal (38 g., 81%), m. p. 104°, was obtained.

1 : 2-*Dideoxy*-D-*galactose*.—(*a*) D-Galactal (0·5 g.) was dissolved in methanol (25 c.c.) and hydrogenated at room temperature with a Raney nickel catalyst. After cessation of the uptake of hydrogen the catalyst was filtered off and the filtrate was evaporated to dryness. The syrupy residue crystallised from aqueous ethanol in plates. 1 : 2-*Dideoxy*-D-*galactose* (0·4 g.) had m. p. 128—129° and $[\alpha]_D^{20}$ +41·8° (*c*, 0·526 in water) (Found : C, 48·7; H, 7·9. $C_6H_{12}O_4$ requires C, 48·6; H, 8·1%). (*b*) 3 : 4 : 6-Triacetyl 1 : 2-dideoxy-D-galactose (1·0 g.) was dissolved in dry methanol (15 c.c.) and sodium (15 mg.) was added. The solution was kept at room temperature for 48 hours and then evaporated to dryness. The residue was extracted with a small amount of ethanol, and the solvent was re-evaporated. Repeated recrystallisation of the product from ethanol afforded 1 : 2-dideoxy-D-galactose identical with the product above. Reacetylation of 1 : 2-dideoxy-D-galactose (1 g.) with acetic anhydride (5 c.c.) in pyridine (10 c.c.) regenerated 3 : 4 : 6-triacetyl 1 : 2-dideoxy-D-galactose, b. p. 120—125° (bath temp.)/1 mm., n_D^{21} 1·4560.

2-*Deoxy*-D-*galactose*.—D-Galactal (6·1 g.) was dissolved in 5% sulphuric acid (85 c.c.) and the solution was kept at 0° for 24 hours. Then the solution was warmed to 60° and neutralised with barium carbonate which was added portionwise. The solution was filtered and decolorised by stirring it with charcoal. It was concentrated under reduced pressure to a syrup which was taken up in methanol (3 vols.) and set aside. 2-Deoxy-D-galactose (4·5 g.) crystallised from solution and was recrystallised from methanol as colourless needles (3·4 g.) which had m. p. 110° and $[\alpha]_D^{21}$ +57° ± 2° (equilibrium) (*c*, 1·0 in water) (Found : C, 43·9; H, 7·1. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3%) [cf. Isbell and Pigman, *J. Res. Nat. Bur. Stand.*, 1939, **22**, 397, who give m. p. 120—121° and $[\alpha]_D$ $+40·8° \longrightarrow +60·5°$ (equilibrium in 30 minutes; *c*, 4·0 in water); Tamm and Reichstein, *loc. cit.*, who give m. p. 105—106° and $[\alpha]_D^{18}$ +60·7° in water]. 2-Deoxy-D-galactose exhibited mutarotation in several solvents :

(*a*) Methanol as solvent (*c*, 0·58) :

Time, mins.	1·5	2·5	5·5	9·5	11·0
$[\alpha]_D^{22}$ ………	+3·44°	+17·25°	+32·2°	+32·2°	+32·2°

(*b*) Water as solvent (*c*, 1·19) :

Time, mins.	2	3	4·5	7	13	19	30	40	46	50
$[\alpha]_D^{17}$ ………	+33·6°	+35·2°	+37°	+38·6°	+46·2°	+50·2°	+54·5°	+56·2°	+57°	+57°

2-*Deoxy*-D-*galactose* 2 : 4-*Dinitrophenylhydrazone*.—2-Deoxy-D-galactose (0·3 g.) in water (10 c.c.) was added to a solution of 2 : 4-dinitrophenylhydrazine (0·7 g.) in glacial acetic acid (10 c.c.), and the mixture was warmed at 90° for 30 minutes. The solvents were then removed under diminished pressure and the residue was crystallised by trituration with ethanol. Recrystallisation from aqueous ethanol gave 2-*deoxy*-D-*galactose* 2 : 4-*dinitrophenylhydrazone*, m. p. 124°, and $[\alpha]_D^{23}$ +30° in methanol (Found : C, 41·5; H, 4·9. $C_{12}H_{16}O_8N_4$ requires C, 41·8; H, 4·7%).

2-*Deoxy*-D-*galactose* p-*Toluidide* [with A. B. FOSTER].—2-Deoxy-D-galactose (0·3 g.) dissolved in ethanol (7 c.c.; 95%) was added to *p*-toluidine (0·23 g., 1·1 mols.), and the solution boiled under reflux for 2 hours. When kept overnight at room temperature the product separated in large prisms. Recrystallisation from ethanol gave 2-*deoxy*-D-*galactose* p-*toluidide* (0·25 g.; 54%) as white prisms, m. p. 142—143°, $[\alpha]_D^{20}$ −149° (*c*, 0·8 in pyridine) (Found : C, 61·9; H, 7·6; N, 5·2. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·5; N, 5·5%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2-*Deoxy*-α-D-*galactose*.—2-Deoxy-D-galactose (0·41 g.) was added to a mixture of freshly distilled acetic anhydride (2·0 g.) in dry pyridine (10 c.c.). The mixture was kept for 2 days and then poured into water. The turbid solution was extracted with chloroform, and the extract washed with dilute sulphuric acid and then water. After being dried ($MgSO_4$) the solvent was evaporated and the residue was distilled. 1 : 3 : 4 : 6-*Tetra-acetyl* 2-*deoxy*-α-D-*galactose* (0·4 g.) was obtained as a thick colourless syrup, b. p. 160—170°/0·01 mm., n_D^{25} 1·4618, $[\alpha]_D^{20}$ +67° in methanol (Found : C, 51·1; H, 6·3. $C_{14}H_{20}O_9$ requires C, 50·6; H, 6·1%).

1 : 3 : 4 : 6-*Tetra-acetyl* 2-*Deoxy*-β-D-*galactose*.—2-Deoxy-D-galactose (0·41 g.), freshly fused and powdered sodium acetate (0·5 g.), and redistilled acetic anhydride (7 c.c.) were heated together under reflux for 30 minutes. The resulting solution was then poured into ice-cold water (100 c.c.) which was extracted with chloroform. The extract was washed with dilute aqueous sodium hydrogen carbonate and with water. After drying ($MgSO_4$) the solvent was removed by evaporation and the residue distilled. 1 : 3 : 4 : 6-*Tetra-acetyl* 2-*deoxy*-β-D-*galactose* (0·5 g.) was obtained as a thick colourless syrup, b. p. 195° (bath temp.)/0·001 mm., n_D^{23} 1·4580, $[\alpha]_D^{20}$ +40·6° in methanol (Found : C, 51·0; H, 6·1%).

2-*Deoxy*-D-*galactose Diethyl Mercaptal*.—Finely divided 2-deoxy-D-galactose (0·5 g.) was added to concentrated hydrochloric acid (0·5 c.c.) at 0°. Ethanethiol (1 c.c.) was added and the mixture was shaken for 4 hours. Water was added and the insoluble material collected. Crystallisation from aqueous ethanol gave 2-*deoxy*-D-*galactose diethyl mercaptal* (0·27 g.), m. p. 107—108°, $[\alpha]_D^{20}$ +40° (*c*, 0·25 in methanol) (Found : C, 44·7; H, 8·0; S, 23·4. $C_{10}H_{22}O_4S_2$ requires C, 44·4; H, 8·2; S, 23·6%).

2-*Deoxy*-D-*galactonolactone*.—2-Deoxy-D-galactose (2·50 g.) was dissolved in water (25 c.c.), and bromine (5 c.c.) was added. The mixture was kept at 37° for 1 day or at room temperature for 1 week. After these periods the solution no longer reduced Fehling's solution. The excess of bromine was removed by aeration and the hydrogen bromide by precipitation with silver carbonate. Silver in solution was removed by treatment with hydrogen sulphide. After filtration through charcoal the solution was evaporated to dryness and the residue triturated with absolute methanol. Crystallisation from dry acetone gave beautiful crystals of 2-*deoxy*-D-*galactonolactone* (1·8 g.), m. p. 97—98°, $[\alpha]_D^{18}$ −12·1° in water (Found : C, 44·4; H, 6·3. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2%). This lactone apparently underwent no hydrolysis in water in 3 days.

2-Deoxy-D-galactonamide.—2-Deoxy-D-galactonolactone (0·45 g.) was dissolved in absolute methanol (10 c.c.) in a Dewar flask. Liquid ammonia was added and the mixture was kept until all the ammonia had evaporated (48 hours). The methanol was evaporated and the syrupy residue was triturated with acetone. After recrystallisation from aqueous acetone, *2-deoxy-D-galactonamide monohydrate* (0·14 g.) was obtained as a colourless powder, m. p. (indefinite) 90—102° with decomposition and evolution of ammonia, $[\alpha]_D^{18}$ +5·3° (*c*, 0·38 in methanol) (Found: C, 36·8; H, 7·4. $C_6H_{13}O_5N,H_2O$ requires C, 36·5; H, 7·6%).

α-Methyl-2-deoxy-D-galactopyranoside.—2-Deoxy-D-galactose (10 g.) was dissolved in 2·5% methanolic hydrogen chloride (200 c.c.) and the reaction was followed polarimetrically. When reaction was complete (2 days), the solution was neutralised with silver carbonate and filtered. The filtrate was evaporated, and on addition of ethyl acetate to the residue part of it crystallised. The solid was separated and repeatedly recrystallised from ethyl acetate. α-Methyl-2-deoxy-D-galactopyranoside (4·2 g.) was obtained as colourless plates, m. p. 112—113°, $[\alpha]_D^{18}$ +169·6° ± 2° (*c*, 0·38 in methanol) (Found: C, 47·2; H, 8·2; OMe, 17·8. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·8; OMe, 17·4%) [cf. Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1640) who give m. p. 109—110° and $[\alpha]_D^{18}$ +71·8° ± 2° in methanol]. To the syrupy product remaining after the separation of the solid α-methyl-2-deoxy-D-galactopyranoside, ethyl acetate was added, and the solution was passed through a column of activated alumina. A syrupy product was isolated, which did not reduce Fehling's solution and was presumably *β-methyl-2-deoxy-D-galactopyranoside* (4 g.), n_D^{19} 1·4869, $[\alpha]_D^{20}$ ±0° in methanol (Found: C, 47·0; H, 7·2; OMe, 17·0. $C_7H_{14}O_5$ requires C, 47·2; H, 7·8; OMe, 17·4%).

Action of Methanolic Hydrogen Chloride on D-Galactal.—D-Galactal (1·66 g.) in 3·3% methanolic hydrogen chloride (10 c.c.) was kept for 1·5 hours, and then the solution was neutralised with silver carbonate. The product was isolated in the manner described above and recrystallised repeatedly from ethyl acetate. *α-Methyl-2-deoxy-D-galactopyranoside* (0·64 g.) was obtained having m. p. 112—113°, $[\alpha]_D^{20}$ +170° (*c*, 0·32 in methanol) (Found: C, 47·2; H, 8·4%).

αβ-Methyl-2-deoxy-D-galactofuranoside.—2-Deoxy-D-galactose (2·5 g.) was dissolved in absolute methanol (60 c.c.), and 5·0% methanolic hydrogen chloride (0·6 c.c.) was added. The reaction ensuing was followed polarimetrically and was arrested at the maximum lævorotatory value by addition of silver carbonate and silver oxide. The solution was filtered through a charcoal pad and then concentrated under diminished pressure. The syrupy residue did not reduce Fehling's solution and was *αβ-methyl-2-deoxy-D-galactofuranoside*, n_D^{22} 1·4828, $[\alpha]_D^{17}$ −68° (*c*, 0·68 in methanol) (Found: C, 48·5; H, 8·3; OMe, 17·7%). Attempts to distil this compound resulted in a change which is being further investigated, but on rapid distillation a small portion did distil [b. p. 170° (bath temp.)/0·001 mm., n_D^{22} 1·4830, $[\alpha]_D^{21}$ −81·2° (*c*, 1·0 in methanol) (Found: C, 46·98; H, 7·8; OMe, 17·0. $C_7H_{14}O_5$ requires C, 47·2; H, 7·8; OMe, 17·4%)].

Treatment of α- and β-Methyl-2-deoxy-D-galactopyranoside with Methanolic Hydrogen Chloride.—(*a*) α-Methyl-2-deoxy-D-galactopyranoside was dissolved in 2% methanolic hydrogen chloride (*c*, 8·0) and the change in optical rotation was observed at intervals. The following results were noted.

Time, mins.	0	5	9	14	20	53	124
$[\alpha]_D^{20}$	+170°	160°	135°	130°	124°	110°	102°

(*b*) A similar procedure was carried out with β-methyl-2-deoxy-D-galactopyranoside. The results obtained were as follows.

Time, mins.	0	5	9	14	22	35	50	80	110
$[\alpha]_D^{20}$	±0°	+10°	47°	53°	64°	80°	90°	96°	98°

Lead Tetra-acetate Oxidations.—(a) *Pyranoside.* α-Methyl-2-deoxy-D-galactopyranoside (0·0278 g.) was dissolved in glacial acetic acid (20 c.c.), and a solution of freshly prepared lead tetra-acetate in glacial acetic acid (25 c.c. of 0·069 N.) was added. The final volume was made up to 50 c.c. with glacial acetic acid. The oxidation was followed titrimetrically by withdrawing 5-c.c. samples at intervals and estimating iodometrically the unused lead tetra-acetate.

Time, hours	0·30	0·45	1·0	1·3	2·18	3·0	4·6	5·4
Uptake of $Pb(OAc)_4$, mol. equiv.	0·40	0·58	0·64	0·82	0·92	1·03	1·15	1·15

(b) *Furanoside.* A similar procedure was carried out on αβ-methyl-2-deoxy-D-galactofuranoside (0·0289 g.), with results as follows.

Time, hours	0·5	1·0	2·0	3·0	5·0	10·0
Uptake of $Pb(OAc)_4$, mol. equiv.	0·10	0·33	0·52	0·70	0·90	1·00

Sodium Metaperiodate Oxidations.—(*a*) αβ-Methyl-2-deoxy-D-galactofuranoside (0·0234 g.) was added to N-sodium hydrogen carbonate (5 c.c.), and 0·173N-sodium metaperiodate (5 c.c.) was added. The mixture was set aside for 2 hours and then sodium arsenite (0·084N.; 15 c.c.) and N-hydrochloric acid (5 c.c.) were added. After the disappearance of the yellow colour, N-sodium acetate (5 c.c.) and a dimedon solution [2 c.c. of a solution of dimedon (0·8 g.) in ethanol (10 c.c.)] were added and the solution was heated at 100° for 10 minutes. After 1 hour the precipitate was collected and weighed after being thoroughly washed with water and dried at 90—95° for 20 minutes. The precipitate (m. p. 189—190°; cf. Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476, who reports m. p. 189—190° for this complex), corresponded in weight (0·04 g.) to the formation of 1 mole of formaldehyde. In a separate experiment it was shown that 1 mole of oxidising agent was consumed by the furanoside in 4 hours.

(*b*) When a similar procedure was carried out with α-methyl-2-deoxy-D-galactopyranoside, no precipitate was formed on addition of the dimedon reagent showing that no formaldehyde had been liberated.

3 : 4 : 6-*Tritoluene*-p-*sulphonyl α-Methyl-2-deoxy*-D-*galactopyranoside*.—α-Methyl-2-deoxy-D-galactopyranoside (0·185 g.) was added to a solution of toluene-*p*-sulphonyl chloride (3·3 mols., 0·7 g.) in dry pyridine (7 c.c.). After being kept for 2 days the solution was poured into ice-water and the precipitate collected. Crystallisation from methanol gave 3 : 4 : 6-*tritoluene*-p-*sulphonyl α-methyl-2-deoxy*-D-*galactopyranoside* (0·25 g.), m. p. 147°, $[\alpha]_D^{18}$ +52° (*c*, 0·076 in methanol) (Found : C, 52·1; H, 4·8. $C_{28}H_{32}O_{11}S_3$ requires C, 52·4; H, 5·0%).

3 : 4 : 6-*Trimethyl α-Methyl-2-deoxy*-D-*galactopyranoside*.—α-Methyl-2-deoxy-D-galactopyranoside (2·8 g.) was added to liquid ammonia (200 c.c.), and sodium (1·5 g.) was added in small pieces. After 20 minutes methyl iodide (15 c.c.) was added. When the liquid ammonia had evaporated, anhydrous magnesium sulphate was added to the residue which was extracted with ether (1 l.). The solvent was evaporated and the syrupy residue was methylated twice more by the same procedure. The crude product obtained was distilled and 3 : 4 : 6-*trimethyl α-methyl-2-deoxy*-D-*galactopyranoside* (0·96 g.) was obtained as a colourless mobile liquid, b. p. 95—105° (bath temp.)/0·001 mm., n_D^{19} 1·4445, $[\alpha]_D^{17\cdot5}$ +138·5° in methanol (Found : C, 54·5; H, 9·2; OMe, 56·7. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·1; OMe, 56·3%).

3 : 4 : 6-*Trimethyl 2-Deoxy*-D-*galactopyranose*.—The fully methylated glycoside (2·8 g.) and N-hydrochloric acid (25 c.c.) were heated together at 70° for 5 hours and at 90° for 1 hour. The hydrolysis was followed polarimetrically and was complete after this time. The solution was neutralised with silver carbonate, filtered, and evaporated. Ethanol was added to the residue which was re-evaporated after filtering. After similar treatment with ether the residue was distilled and 3 : 4 : 6-*trimethyl 2-deoxy*-D-*galactopyranose* (0·518 g.) obtained as a clear colourless viscous liquid, b. p. 150—160° (bath temp.)/0·001 mm., n_D^{22} 1·4637, $[\alpha]_D^{24}$ +41° in methanol (Found : C, 52·2; H, 8·2; OMe, 43·4. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

3 : 4 : 6-*Trimethyl 2-Deoxy*-D-*galactonolactone* (*δ-Type*).—3 : 4 : 6-Trimethyl 2-deoxy-D-galactopyranose (0·36 g.) in aqueous solution (15 c.c.) and bromine (3 c.c.) were kept at 37° for 3 days. The excess of bromine was removed by aeration, and hydrogen bromide by silver oxide. Passage of hydrogen sulphide removed silver ions in solution. After filtration the solution was evaporated to dryness and the residue distilled. 3 : 4 : 6-*Trimethyl 2-deoxy*-D-*galactonolactone* was obtained as a colourless liquid, b. p. 154—161° (bath temp.)/0·001 mm., $[\alpha]_D^{18}$ +81·7° in water (Found : C, 52·3; H, 8·0; OMe, 45·6. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9; OMe, 45·1%). Polarimetric observations indicated that in aqueous solution (*c*, 1·125) it was hydrolysed in 4 days.

Time, hours	0	1	6	22	30	47	72	103	130
$[\alpha]_D^{18}$	+82°	75°	63°	51°	46°	41°	32°	22°	22°

3 : 5 : 6-*Trimethyl αβ-Methyl-2-deoxy*-D-*galactofuranoside*.—αβ-Methyl-2-deoxy-D-galactofuranoside (1·6 g.) was added to liquid ammonia (200 c.c.), and then sodium (1·2 g.) was added. After 20 minutes methyl iodide (8 c.c.) was added. The product was isolated as already described and was methylated twice more. 3 : 5 : 6-*Trimethyl αβ-methyl-2-deoxy*-D-*galactofuranoside* (0·64 g.) was obtained as a pale straw-coloured liquid, b. p. 130—135° (bath temp.)/12 mm., n_D^{22} 1·4421, $[\alpha]_D^{21}$ −29·7° in water (Found : C, 54·3; H, 9·4; OMe, 54·7. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·1; OMe, 56·3%).

3 : 5 : 6-*Trimethyl 2-Deoxy*-D-*galactofuranose*.—3 : 5 : 6-Trimethyl αβ-methyl-2-deoxy-D-galactofuranoside (0·47 g.) and 0·01N-hydrochloric acid (45 c.c.) were heated together under reflux for 20 minutes. After neutralisation (Ag_2CO_3) and filtration the solution was concentrated under diminished pressure. Addition of ethanol served to remove colloidal silver. After filtration, benzene was added and the solution concentrated. Distillation of the residue gave 3 : 5 : 6-*trimethyl 2-deoxy*-D-*galactofuranose* (0·375 g.) as a clear, thick syrup, which strongly reduced Fehling's solution, m. p. 105—110° (bath temp.)/0·001 mm., n_D^{20} 1·4535, $[\alpha]_D^{19}$ −35·1° (*c*, 2·05 in methanol), $[\alpha]_D^{21}$ −24° (*c*, 1·0 in water; mutarotation complete in 7 minutes) (Found : C, 52·5; H, 8·8; OMe, 46·0. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

3 : 5 : 6-*Trimethyl 2-Deoxy*-D-*galactonolactone* (*γ-Type*).—3 : 5 : 6-Trimethyl 2-deoxy-D-galactofuranose (0·15 g.) in water (5 c.c.) was treated with bromine (1 c.c.) for 2 weeks. The product was isolated in the usual manner, and 3 : 5 : 6-*trimethyl 2-deoxy*-D-*galactonolactone* (46 mg.) was obtained as a colourless liquid, b. p. 140—151° (bath temp.)/0·001 mm., n_D^{19} 1·4520 (Found : C, 52·2; H, 8·2; OMe, 43·8. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9; OMe, 45·1%).

Polarimetric observations on an aqueous solution of this lactone indicated that no detectable hydrolysis occurred in over 100 hours.

Time, hours	0·5	4·5	21·5	68·75	93·75	110
$[\alpha]_D^{18}$	−24·9°	−24·9°	−25°	−25·6°	−25°	−25·8°

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THE CHEMISTRY DEPARTMENT,
THE UNIVERSITY, BIRMINGHAM.

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132. 1 : 2 : 5 : 6-*Tetrahydropyridine: Isolation from Technical Piperidine by Efficient Fractional Distillation.*

By W. H. Davies and L. L. McGee.

Technical piperidine has been fractionally distilled and found to contain some water, about 20% of 1 : 2 : 5 : 6-tetrahydropyridine, b. p. 117·4°/771 mm., and only 70% of piperidine, b. p. 106°. The unsaturated base was identified by a series of derivatives. Traces of α-picoline and tetrahydropicolines have also been found in some samples.

For over 40 years, and from different countries, there have been reports that technical piperidine, presumably prepared by reduction of pyridine, usually contains unsaturated impurities. When pure piperidine has been required, it has been obtained by making an *N*-derivative, *e.g.*, the nitroso- (Vorländer and Wallis, *Annalen*, 1906, **345**, 277) or the benzoyl (Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, *B*, 60) derivative, oxidising away the unsaturated material with permanganate in acetone, and hydrolysing off the protecting group.

Reduction of alkyl-substituted pyridines with sodium in alcohol is known to give tetrahydro-derivatives which appear to be Δ^1- or Δ^2-isomers (Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 508: Koenigs *et al.*, *Ber.*, 1905, **38**, 3042, 3928; 1907, **40**, 3199). Marie and Lejeune (*J. Chim. physique*, 1925, **22**, 59) stated that electrolytic reduction of pyridine gave piperidine in about 65% yield together with about 20% of tetrahydropyridine. The evidence for the latter was that a semi-crystalline mass separated from the distillation residue; this was assumed to be "dipiperidein," the dimer of 2 : 3 : 4 : 5-tetrahydropyridine previously obtained by Lellman and Schwaderer (*Ber.*, 1889, **22**, 1319) by the action of alkali on *N*-chloropiperidine. In a patent (Tech. Res. Works, B. P. 309,300) it is reported that hydrogenation of pyridine over nickel at 180°/300 lb. gives 80% of piperidine and about 10% of tetrahydropyridine, b. p. 93—95°. Again, no evidence was given that the product was a tetrahydropyridine; the low boiling point is surprising and suggests that this fraction may have been the piperidine–water azeotrope, b. p. 92·8° (cf. Horsley, *Ind. Eng. Chem.*, *Anal.*, 1947, **19**, 508). Apart from this work, the compounds responsible for the unsaturation in technical piperidine have not, so far as we are aware, been isolated or characterised.

As we required pure piperidine, we examined several samples of commercially available piperidine. Material sold as 96% piperidine was slightly yellow and a "pure" sample, sold as 98—99% piperidine, was water-white; apart from this yellow impurity, the samples seemed to be identical and the "pure" was probably obtained by total distillation of the 96% material. Samples of both types were found to have b. p. 106° (by direct determination) but by good fractionation gave three main products: (i) 6%, b. p. 92° (piperidine–water azeotrope; cf. Horsley, *loc. cit.*), (ii) 70%, b. p. 106° (pure piperidine), and (iii) 20%, b. p. 117°. (These percentages are roughly corrected for the losses in the intermediate fractions.) A very small and variable amount of higher-boiling bases, mainly b. p. 123°, was also obtained in some cases. The 117° fraction was freed from traces of pipecolines (methylhexahydropyridines) by azeotropic distillation.

The infra-red absorption spectrum of the base of b. p. 117° showed that it was free from pyridine, picolines, and pipecolines. Analysis of the base itself and of its *acetyl* and *benzoyl* derivatives (from which the base could be regenerated) agreed with the empirical formula C_5H_9N, *i.e.*, a tetrahydropyridine. Hydrogenation over Raney nickel resulted in absorption of 1 mole of hydrogen to give piperidine (identified by physical constants and its benzoyl derivative).

The three tetrahydropyridines have previously been reported. The base, b. p. 117°, cannot be the 2 : 3 : 4 : 5-tetrahydro-compound because it forms *N*-acyl derivatives. The 1 : 2 : 3 : 4-tetrahydro-isomer [obtained by caustic fusion of "*N*-oxypiperidine" (Wolffenstein, *Ber.*, 1892, **25**, 2783) or piperidine-2-sulphonic acid (Paal and Hubaleck, *Ber.*, 1901, **34**, 2761)] gives an oily benzoyl derivative and a hydrochloride, m. p. 230° (decomp.); the m. p.s of the corresponding derivatives of the base, b. p. 117°, were 60—62° and 191—193° (decomp.). The 1 : 2 : 5 : 6-tetrahydropyridine has been prepared by Renshaw and Conn (*J. Amer. Chem. Soc.*, 1938, **60**, 745) by treating 4-bromopiperidine with sodium methoxide. They reported m. p.s (or decomposition points) for the hydrochloride, aurichloride, platinichloride, and *N*-methyl methiodide (*i.e.*, 1 : 1-dimethyl-1 : 2 : 5 : 6-tetrahydropyridinium iodide) in close agreement with those of the corresponding derivatives of our base, b. p. 117°, which is therefore, beyond doubt, 1 : 2 : 5 : 6-tetrahydropyridine. Renshaw and Conn did not isolate the free base because of its "ready polymerisation;" we find, on the other hand, that the free base is stable under ordinary conditions and can be distilled without appreciable polymerisation.

The amount of the higher-boiling fraction, b. p. 123°, varied with different samples of technical piperidine and was in all cases very small. Infra-red absorption spectra indicated the presence of *C*-methyl groups and unsaturation. From chemical evidence, this fraction was clearly a mixture. On conversion into its picrate, a mixture was formed from which α-picoline picrate was isolated in 17% yield. After mild hydrogenation, α-picoline was again isolated as its picrate (in 14% yield) and α-pipecoline as its *benzenesulphonyl* derivative. It is probable, therefore, that the fraction of b. p. 123° is a mixture of α-picoline (about 20%) and one or more of its tetrahydro-derivatives (about 80%), these properties being in agreement with the picoline isolated as picrate and with the hydrogen absorption.

Catalytic hydrogenation of pyridine over Raney nickel and over nickel on kieselguhr was examined but there was no appreciable formation of 1 : 2 : 5 : 6-tetrahydropyridine. Not all samples of commercially available piperidine contained the unsaturated base, and it seems possible that it is only present when the " piperidine " is manufactured by electrolytic reduction of pyridine. It is curious that the mixture in this technical piperidine should have approximately the correct b. p. for pure piperidine (106°) : presumably the water and the tetrahydropyridine balance the b. p. to give this fortuitous result.

EXPERIMENTAL.

Distillation of Technical Piperidine.—The following is a typical batch run. A column (14" × ⅝") packed with $\frac{1}{16}$" × $\frac{1}{16}$" stainless-steel gauze rings was used : theoretical plates at total reflux, 46 ; at 10 c.c. per hour take-off rate, 30 (approx.) ; at 20 c.c. per hour take-off, 20 (approx.). Pressure, 756·5 mm. Charge : 200 c.c. of good-quality technical piperidine (sold as 95·5% piperidine).

Fraction no.	Temp.	Vol. (c.c.).	% of total.	Take-off rate (c.c./hr.).	Reflux ratio
1	92°	10	5	10	30 : 1
2	92—106	3·0	1·5	10	30 : 1
3	106	125·0	62·5	20	15 : 1
4	106—117	13·4	6·7	10	30 : 1
5	117	33·5	16·7	20	15 : 1
Residue	—	11·0	—	—	—
Column hold-up	—	5·0	—	—	—

Fraction 1 was the azeotrope of piperidine (65%) and water (cf. Horsley, *loc. cit.*). After this fraction had been dried (KOH), infra-red absorption spectra indicated that it was mainly piperidine and that it was substantially free from pipecolines (azeotrope, b. p. 92—93°). The total piperidine content (fractions 1—3) was about 70%.

Fraction 5 was 1 . 2 : 5 : 6-tetrahydropyridine, the content of which in the technical piperidine must be about 20%.

Purification of 1 : 2 : 5 : 6-*Tetrahydropyridine.*—The base (fraction 5, above; 45 c.c.) and water (10 c.c.) were distilled to give fractions : (i) b. p. 92—93° (3%), (ii) b. p. 95° (26%), and (iii) b. p. 117° (20%). At this point, a further 5 c.c. of water was added and the distillation continued to give the azeotrope of 1 : 2 : 5 : 6-tetrahydropyridine, b. p. 95°, identical with fraction (ii). The azeotrope was dried (KOH) and distilled, to give 1 : 2 : 5 : 6-*tetrahydropyridine*, b. p. 117°, m. p. −48° (Found : C, 71·85 ; H, 10·65 ; N, 16·6. C_5H_9N requires C, 72·16 ; H, 10·8 ; N, 16·8%).

Fraction (i) was shown to be an azeotrope in which pipecolines were identified by infra-red absorption. Similar results were obtained with other samples of technical piperidine.

B. p. Determinations.—Technical piperidine, 105·6° ; pure piperidine, 105·6° ; 85% piperidine +15% 1 : 2 : 5 : 6-tetrahydropyridine (water-free), 106·7°.

Derivatives of 1 : 2 : 5 : 6-*Tetrahydropyridine.*—*Acetyl* (by refluxing in acetic anhydride), b. p. 117°/19 mm., n_D^{23} 1·4985, m. p. *ca.* −3° (Found : N, 11·3. $C_7H_{11}ON$ requires N, 11·2%). *Benzoyl* (by Schotten–Baumann method), b. p. 113°/0·15 mm., m. p. 60—62° (from light petroleum) (Found : C, 76·7 ; H, 6·95 ; N, 7·65. $C_{12}H_{13}ON$ requires C, 77·0 ; H, 7·0 ; N, 7·5%). *Picrate*, m. p. 161—163° (from water) (Found : N, 17·7. $C_5H_9N,C_6H_3O_7N_3$ requires N, 17·9%). Hydrochloride (from ethanol), m. p. 191—193° (Found : Cl', 29·3. Calc. for C_5H_9N,HCl : Cl', 29·7%). Aurichloride, m. p. 141—142° (decomp.). Platinichloride, m. p. 187—188° (m. p. depends on rate of heating). Metho-methiodide, m. p. 274—275° (decomp.) (Found : I', 53·0. Calc. for $C_6H_{11}N,CH_3I$: I', 53·1%). For the corresponding last four derivatives of 1 : 2 : 5 : 6-tetrahydropyridine, Renshaw and Conn (*loc. cit.*) give m. p. 188—189°, 141° (decomp.), 187—188° (decomp.), and 274—275°, respectively.

Base of B. p. 123°.—This was obtained by fractionating the higher-boiling residues from a number of distillations of technical piperidine. The crude picrate, prepared in water, had m. p. 133—144° and was crystallised from water to give α-picoline picrate (17%), m. p. (alone or mixed with an authentic sample) 164—166° (Found : C, 44·7 ; H, 3·1 ; N, 17·3. Calc. for $C_6H_7N,C_6H_3O_7N_3$: C, 44·7 ; H, 3·1 ; N, 17·4%) ; the *benzenesulphonyl* derivative (prepared by the Schotten–Baumann method) had m. p. 67—69° (from methanol) (Found : C, 60·4 ; H, 6·1 ; N, 5·7. $C_{12}H_{15}O_2NS$ requires C, 60·8 ; H, 6·3 ; N, 5·9%). This is a derivative of a methyltetrahydropyridine but the positions of the methyl group and double bond were not established.

The base of b. p. 123° (2 g.) in dioxan (15 c.c.) was hydrogenated at ordinary temperature and pressure over platinum (0·2 g.) (Hydrogen absorption : 380 c.c. Calc. for $C_6H_{11}N$, 460 c.c. Calc. for 80% $C_6H_{11}N$, 370 c.c.). On conversion of part of the reduced base into its picrate, a mixture was obtained from which α-picoline picrate was isolated in 14% yield. The rest of the reduced base was treated with benzenesulphonyl chloride under Schotten–Baumann conditions to give N-*benzenesulphonyl-α-pipecoline* (30%), m. p. 64—66° (from light petroleum), alone or mixed with an authentic sample (Found : C, 60·25; H, 6·75; N, 5·7. $C_{12}H_{17}O_2NS$ requires C, 60·3; H, 7·1; N, 5·9%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH LABORATORIES,
HEXAGON HOUSE, BLACKLEY, MANCHESTER.

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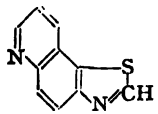
133. *Some Naphthothiazoles.*

By W. A. BOGGUST, WESLEY COCKER, J. C. P. SCHWARZ, and E. R. STUART.

Naphtho(1′ : 2′-4 : 5)thiazole and *naphtho*(2′ : 1′-4 : 5)*thiazole* have been prepared and their light-absorption characteristics compared with those of pyridino(2′ : 3′-6 : 7)benzthiazole. Attempts to prepare naphtho(2′ : 3′-4 : 5)thiazole are described.

RECENTLY Cocker and Boggust (*J.*, 1949, 355) described a new quinthiazole which was assumed to be the angular compound, pyridino(2′ : 3′-6 : 7)benzthiazole (I). Two angular naphthothiazoles have now been prepared for comparison of their light-absorption properties with those of the quinthiazole. These compounds, naphtho(1′ : 2′-4 : 5)thiazole (II) and *naphtho*(2′ : 1′-4 : 5)*thiazole* (III), were obtained by the route used by Mercury, Vincent, and Sherrill (*J. Amer. Chem. Soc.*, 1946, **68**, 1594) which involves oxidative ring closure of the appropriate naphthylthio-oxamic acid to the corresponding naphthothiazole-2-carboxylic acid which is then decarboxylated. The naphthothiazole (II) had previously been obtained by Hofmann (*Ber.*, 1887, **20**, 1798, 2265) from formo-α-naphthylamide and sulphur. The compound (III) was also obtained by an alternative method described below.



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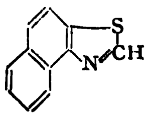

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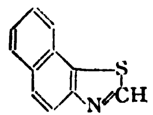

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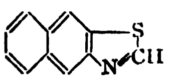

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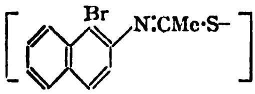

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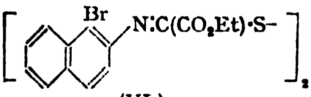

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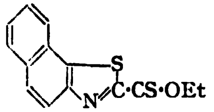
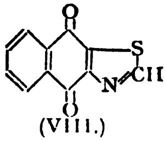


(VII.)



(VIII.)

All attempts to prepare naphtho(2′ : 3′-4 : 5)thiazole (IV) were unsuccessful. Attempted cyclisation of 1-*bromo*-2-*naphthylthio-oxamic acid* or its *ethyl* ester, obtained by thionation of *ethyl* 1-*bromo*-2-*naphthyloxamate* in toluene, yielded a product which on heating with mineral acid gave 1-bromo-2-naphthylamine. A similar experience was recorded by Levkoev and Baskirova (*Chem. Abstr.*, 1947, **41**, 447) who showed that 1-bromo-2-thioacetamidonaphthalene on oxidation yielded the disulphide (V), which gave 1-bromo-2-naphthylamine when heated with mineral acid. These workers also showed that the " linear naphthothiazole " of Fries and Buchler (*Annalen*, 1927, **454**, 260) prepared by oxidation of 1-bromo-2-thiobenzamidonaphthalene is, in reality, a similar disulphide. When ethyl 1-bromo-2-naphthyloxamate was thionated in boiling xylene it yielded a mixture of an unidentified, sparingly soluble compound which may be the *disulphide* (VI) and *ethyl naphtho*(2′ : 1′-4 : 5)*thiazole-2-thioncarboxylate* (VII) (the latter being produced with elimination of bromine). (VII) was hydrolysed to *sodium naphtho*(2′ : 1′-4 : 5)*thiazole-2-carboxylate*, and this gave the parent thiazole (III) when boiled with acid.

Naphtho(2′ : 3′-4 : 5)*thiazole*-1′ : 4′-*quinone* (VIII) was prepared by condensation of 2-amino-1 : 4-naphthaquinone-3-thiol with formaldehyde in weakly acid solution (cf. B.P. 262,141/1926), the resulting thiazoline being spontaneously oxidised during isolation as shown by the fact that the product is unaffected by hydrogen peroxide. All attempts to reduce the quinone to the naphthothiazole were unsuccessful.

We were unable to obtain 2-methylnaphtho(2′ : 3′-4 : 5)thiazole by the method of B.P. 445,538, as in our hands the preparation of 2-aminonaphthalene-3 : 6-disulphonyl chloride recorded there failed. Further attempted deamination of 1-bromo-2-aminonaphtho(2′ : 3′-4 : 5)thiazole (Hunter and Jones, *J.*, 1930, 941) gave unpromising results.

Ultra-violet light absorption data are as follows :

Compound :	(I).		(II).		(III).	
	$\lambda_{\text{max.}}$, A.	log ε.	$\lambda_{\text{max.}}$, A.	log ε.	$\lambda_{\text{max.}}$, A.	log ε.
	2500	4·35	2310	4·80	2300 2500	4·35 4·60
	(2900	3·7)	2900	3·93	2800 2900	3·75 3·73
	3320	3·31	3250	3·09	3200 3350	2·79 2·81

The higher degree of resolution apparent in (III) is in accordance with previous experimental evidence that addition of an auxochrome or chromophore in the 2-position in naphthalene produces a more complex spectrum than does substitution in the 1-position (Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; A.P.I. Research Project 44 Nat. Bur. Stand. Catalog of U.V. Spectral Data, Serial Nos. 244—247, 1- and 2-naphthols, contributed by U.O.P. Co., Riverside, Illinois; Cocker *et al.*, to be published).

Naphtho(2′ : 3′-4 : 5)thiazole-1′ : 4′-quinone shows maxima at 2450 A. (log ε 4·45), 2800 A. (log ε 4·20), and 3400 A. (log ε 3·52), characteristic of tricyclic quinones (Spruit, *Rec. Trav. chim.*, 1949, **68**, 325).

All light-absorption measurements were made in alcoholic solution using the Beckman model DU quartz spectrophotometer.

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss.)

Naphtho(1′ : 2′-4 : 5)*thiazole* (II).—Ethyl 1-naphthyloxamate was obtained substantially as described by Ballo (*Ber.*, 1873, **6**, 247).

1-*Naphthylthio-oxamic acid*. The above oxamic ester (11 g.) in boiling anhydrous xylene (220 c.c.) was slowly treated with phosphorus pentasulphide (6·9 g.), and refluxing was continued for 1 hour. The hot xylene was decanted from some tarry material and was distilled in steam, leaving an oily residue consisting of the thio-ester, which was shaken with an excess of cold 10% sodium hydroxide solution until a clear solution was obtained. After filtration, the solution was acidified and the *thio-oxamic acid* (10 g.; m. p. 117°) was crystallised from light petroleum (b. p. 60—80°) as yellow needles, m. p. 124—125° (Found : C, 62·4; H, 4·2. $C_{12}H_9O_2NS$ requires C, 62·4; H, 3·9%).

Naphtho(1′ : 2′-4 : 5)*thiazole*. A filtered solution of the crude thio-oxamic acid (10 g.) in 10% sodium hydroxide solution (330 c.c.) was stirred and slowly treated with a solution of potassium ferricyanide (75 g.) in water (180 c.c.). The yellowish-brown precipitate which formed was collected and immediately refluxed with 8% hydrochloric acid (150 c.c.) for 1 hour. The hot solution was filtered from Prussian blue, boiled with charcoal, and filtered. On cooling, the hydrochloride of the required thiazole was obtained (5·5 g.). It readily dissociated when heated or in water, but crystallised satisfactorily from concentrated hydrochloric acid as pale yellow needles, m. p. 185°. The hydrochloride (5·0 g.), basified with aqueous ammonia, yielded the thiazole (2·9 g.) which crystallised from light petroleum (b. p. 40—60°) as large, pale yellow prisms, m. p. 53—54° (cf. Hofmann, *loc. cit.*, who gives m. p. 45—46°) (Found : C, 71·0; H, 4·0. Calc. for $C_{11}H_7NS$: C, 71·3; H, 3·8%).

Naphtho(2′ : 1′-4 : 5)*thiazole* (III).—Ethyl 2-naphthyloxamate was obtained as described by Meyer and Muller (*Ber.*, 1897, **30**, 770).

2-*Naphthylthio-oxamic acid*. This was prepared from ethyl 2-naphthyloxamate (11 g.) as described for the 1-isomer. A small sample crystallised from water as yellow, glistening plates, m. p. 269—271°, but a satisfactory analysis was not obtained.

Naphtho(2′ : 1′-4 : 5)*thiazole*. The foregoing crude thio-oxamic acid was treated as in the preparation of (II). The hydrochloride of the required thiazole was not isolated, but its clarified solution (charcoal) in 10% hydrochloric acid was basified with aqueous ammonia, and the *product* (3·4 g.; m. p. 60°) crystallised from dilute alcohol as colourless plates or needles, m. p. 65° (Found : C, 70·8; H, 3·6%).

Ethyl 1-*Bromo*-2-*naphthyloxamate*.—Ethyl 2-naphthyloxamate (24·5 g.) was brominated in the minimum quantity of cold chloroform with bromine (5·5 c.c.) in chloroform (15 c.c.). After 1 hour, the chloroform was removed in a vacuum, and the crude ester was washed with aqueous sodium carbonate and crystallised from alcohol as colourless needles (27·5 g.), m. p. 98—99° (Found : C, 52·2; H, 3·7. $C_{14}H_{12}O_3NBr$ requires C, 52·2; H, 3·7%). The compound was also obtained when 1-bromo-2-naphthylamine was refluxed for 1 hour with ethyl oxalate.

Thionation, in Xylene, of Ethyl 1-*Bromo*-2-*naphthyloxamate*.—The compound (16·6 g.) in boiling anhydrous xylene (350 c.c.) was slowly treated with phosphorus pentasulphide (11·5 g.), and refluxing was continued for 45 minutes. Hydrogen bromide was evolved, especially during the later stages of the reaction. The hot xylene was decanted and cooled, yielding a yellow solid (*A*; 4·5 g.), m. p. 100—230°. On extraction with ether, (*A*) left a residue (*B*; 3·3 g.), m. p. 250—275° (according to the rate of heating) which crystallised from xylene as red needles. After melting, it resolidified and then gave m. p. 328—331°. We were unable to identify (*B*), but it may be the *disulphide* (VI) (Found : C, 49·6; H, 2·7. $C_{28}H_{22}O_4N_2S_2Br_2$ requires C, 49·8; H, 3·3%), since it is sparingly soluble in organic solvents, *e.g.*, ethanol, ethyl acetate, and benzene, requiring boiling xylene for recrystallisation, and thus probably has a relatively high molecular weight. The mother-liquor from (*A*) was evaporated in a vacuum to 50 c.c. and cooled, whereupon yellow crystals (*C*) were deposited. The mother-liquor from (*C*) was evaporated to dryness in a vacuum, and the resulting tarry solid crystallised from dilute alcohol as yellow needles

(2·9 g.), m. p. 100—110° (according to rate of heating), consisting of *ethyl naphtho*(2′ : 1′-4 : 5)*thiazole-2-thioncarboxylate* (VII) (Found : C, 61·4; H, 4·1; S, 21·1. $C_{14}H_{11}ONS_2$ requires C, 61·5; H, 4·0; S, 23·4%). Extraction of (*C*) with ether gave a further 1 g. of the thion-ester. The ester (VII) (0·5 g.) was heated for 10 minutes with 10% aqueous sodium hydroxide (2·0 c.c.) in water (100 c.c.), and the hot solution was filtered and cooled, yielding *sodium naphtho*(2′ : 1′-4 : 5)*thiazole-2-carboxylate* as colourless plates, m. p. 350—355° (Found : S, 11·6. $C_{12}H_6O_2NSNa,H_2O$ requires S, 11·9%). The salt was boiled for 90 minutes with 15% hydrochloric acid, and the hot solution was filtered, cooled, and basified with aqueous ammonia, giving naphtho(2′ : 1′-4 : 5)thiazole (0·2 g.), identical with that prepared by the previous method.

Ethyl 1-*Bromo*-2-*naphthylthio-oxamate*.—Ethyl 1-bromo-2-naphthyloxamate (22·5 g.) in boiling anhydrous toluene (550 c.c.) was stirred with phosphorus pentasulphide (18 g.) under reflux for 90 minutes and then filtered. On cooling, the filtrate deposited yellow crystals, m. p. 275°, identical with (*B*). The mother-liquor was evaporated to dryness in a vacuum, leaving a yellow solid (23 g.), m. p. 75—78°, which was crystallised several times from alcohol, to give the required *thio*-ester as yellow needles, m. p. 88° (Found : C, 49·6; H, 4·5. $C_{14}H_{12}O_2NSBr$ requires C, 49·7; H, 3·6%).

1-*Bromo*-2-*naphthylthio-oxamic Acid*.—Ethyl 1-bromo-2-naphthylthio-oxamate (1 g.) was shaken with cold 10% potassium hydroxide solution (10 c.c.) for 2 hours. The salt was collected and shaken for 30 minutes with dilute hydrochloric acid, and the precipitated *acid* (0·8 g.) crystallised from dilute alcohol as golden needles, m. p. 123° (decomp.) (Found : C, 45·3; H, 3·3. $C_{12}H_8O_2NSBr$ requires C, 46·5; H, 2·6%).

Naphtho(2′ : 3′-4 : 5)*thiazole*-1′ : 4′-*quinone* (VIII).—2-Chloro-3-amino-1 : 4-naphthaquinone (36 g.) was refluxed with sodium sulphide (45 g.) in water (330 c.c.) for 25 minutes. To the resultant deep-blue solution, formaldehyde (40%; 72 c.c.) was added, followed by glacial acetic acid (36 c.c.) diluted with water (72 c.c.). The mixture was refluxed for 1 hour and filtered. The black residue was extracted several times with boiling alcohol (500 c.c.). On cooling, *naphtho*(2′ : 3′-4 : 5)*thiazole*-1′ : 4′-*quinone* (13 g.), m. p. 245—252°, was deposited. The m. p. was not raised above 245—252° by repeated crystallisation (Found : C, 61·3; H, 2·4; N, 6·5. $C_{11}H_5O_2NS$ requires C, 61·4; H, 2·3; N, 6·5%).

Attempts to reduce this quinone to the parent naphthothiazole by zinc dust distillation in hydrogen, zinc dust fusion (Clar, *Ber.*, 1939, **72**, 1645), stannous chloride in acetic acid (Fries and Kerkow, *Annalen*, 1922, **427**, 281), or hydrogen iodide and phosphorus were unsuccessful.

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UNIVERSITY CHEMICAL LABORATORY,
TRINITY COLLEGE, DUBLIN.

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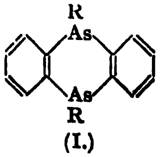
134. *A Synthesis of Derivatives of* o-*Phenylene-ethylenediarsine and of* o-*Phenylenetrimethylenediarsine.*

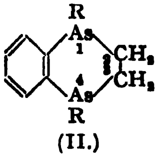
By R. H. GLAUERT and FREDERICK G. MANN.

Derivatives of the above two novel heterocyclic ring systems can readily be obtained from *o*-phenylenebisdimethylarsine, which combines with ethylene dibromide to give 1 : 1 : 4 : 4-tetramethyl-*o*-phenylene-ethylenediarsonium dibromide, and with trimethylene dibromide to give 1 : 1 : 5 : 5-tetramethyl-*o*-phenylenetrimethylenediarsonium dibromide. The thermal decomposition of these salts is being investigated.

IN view of the fact that the heterocyclic ring system of the 5 : 10-disubstituted 5 : 10-dihydroarsanthrens (I) can be reasonably readily synthesised and has high stability (Kalb, *Annalen*, 1921, **423**, 74; Chatt and Mann, *J.*, 1940, 1184), it is surprising that the similar but simpler systems present in the 1 : 4-disubstituted *o*-phenylene-ethylenediarsines (1 : 4-diarsatetrahydronaphthalenes) (II) and in the 1 : 4-disubstituted diethylenediarsines (1 : 4-diarsa*cyclo*hexanes) (III) have hitherto not been recorded. We are engaged in the systematic study of the systems (II) and (III) and of their derivatives, and the present paper records briefly one ready synthesis of the heterocyclic system (II) and of analogous compounds.

For this synthesis we have utilised *o*-phenylenebisdimethylarsine (IV), prepared by the method of Chatt and Mann (*J.*, 1939, 610). This diarsine appeared to be particularly promising


(I.)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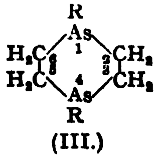
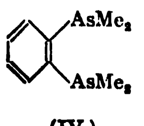
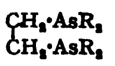

(III.)


(IV.)

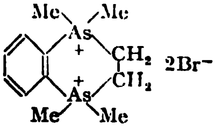


$$\begin{matrix}CH_2\cdot AsR_2\\ |\\ CH_2\cdot AsR_2\end{matrix}$$

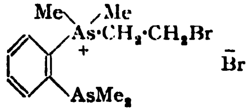
(V.)

for our purpose, for the two tertiary arsine groups are known to be highly reactive, since Chatt and Mann (*J.*, 1939, 1622) and Allison and Mann (*J.*, 1949, 2915) have shown that the diarsine has strongly chelating properties. Furthermore, it was considered that a diarsine of this type would lend itself more readily to the projected cyclisation than, for example, the corresponding ethylenebisdialkylarsines (V) (Chatt and Mann, *loc. cit.*), because in the former compound the two tertiary arsenic atoms are held rigidly by the *o*-phenylene group in precisely the position required for ring formation.

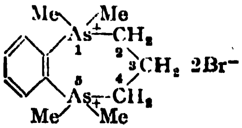
Experiment has confirmed these considerations. We find that, when the diarsine (IV) is heated with one molecular equivalent of ethylene dibromide, combination readily occurs to give the highly crystalline *dimethobromide* (VI) of 1 : 4-dimethyl-*o*-phenylene-ethylenediarsine, *i.e.*, 1 : 1 : 4 : *4-tetramethyl-*o*-phenylene-ethylenediarsonium dibromide* (1 : 1 : 4 : *4-tetramethyl-*1 : 2 : 3 : *4-tetrahydro-*1 : *4-diarsonianaphthalene dibromide*), m. p. 255°. Evidence that cyclisation has in fact occurred and that the product is not the isomeric monoarsonium bromide (VII) is provided in two ways : (*a*) volumetric analysis of a cold aqueous solution of the compound shows that all the bromine is present in the ionic form, and (*b*) the addition of aqueous sodium picrate to such a solution causes the immediate precipitation of the corresponding *dimethopicrate*.



(VI.)



(VII.)



(VIII.)

This type of cyclisation is not limited to the formation of six-membered ring systems. We find that the diarsine (IV) when similarly heated with trimethylene dibromide readily gives the highly crystalline bicyclic *dimethobromide* (VIII), *i.e.*, 1 : 1 : 5 : *5-tetramethyl-o-phenylenetrimethylenediarsonium dibromide* (1 : 1 : 4 : *4-tetramethyl-*1 : *4-diarsonia-*2 : *3-benz*cyclo*hept-2-ene dibromide*), m. p. 258°. Here again cyclisation is confirmed by determination of ionic bromine, and by conversion of the dibromide in cold aqueous solution into the corresponding *dimethopicrate*. There is little doubt that, particularly in the seven-membered ring system present in the compound (VIII), the polymethylene chain is " buckled " and that a stable and probably almost strainless ring is thus produced.

It is significant that both the dimethobromides (VI) and (VIII) melt with effervescence. A preliminary investigation of the thermal decomposition of the dimethobromide (VI) indicates that more than one tertiary arsine may thus be formed. We are now investigating this decomposition on a larger scale because the expected simple loss of methyl bromide would give rise to 1 : 4-dimethyl-*o*-phenylene-ethylenediarsine, which should then be capable of conversion into a tricyclic diarsine system by further combination with ethylene dibromide—a synthesis which would be precisely analogous to Mann and Mukherjee's synthesis of the dimethobromide of triethylenediamine by the combination of 1 : 4-dimethylpiperazine and ethylene dibromide (*J.*, 1949, 2298).

EXPERIMENTAL.

o-*Phenylenebisdimethylarsine* (IV).—By working in an atmosphere of nitrogen, as Chatt and Mann (*loc. cit.*) recommend, this diarsine was prepared from *o*-phenylenebisdichloroarsine, in 82% yield, as a colourless liquid, b. p. 146°/15 mm.

1 : 1 : 4 : *4-Tetramethyl-*o*-phenylene-ethylenediarsonium Dibromide* (1 : 1 : 4 : *4-Tetramethyl-*1 : 2 : 3 : *4-tetrahydro-*1 : *4-Diarsonianaphthalene Dibromide*) (VI).—A mixture of the diarsine (IV) (2·7 g.) and dry ethylene dibromide (1·8 g., 1 mol.) was heated under nitrogen at 125—130°, *i.e.*, at just below the b. p. of the dibromide. The mixture soon solidified and after a further 2 hours' heating was cooled, pulverised, washed with ether, and recrystallised from methyl alcohol. The *dibromide* (VI) was obtained as white crystals, m. p. 255° (effervescence) (Found : C, 30·1; H, 4·8; ionic Br, 33·0. $C_{12}H_{20}Br_2As_2$ requires C, 30·4; H, 4·3; ionic Br, 33·7%). The dibromide is freely soluble in cold water, moderately soluble in boiling methyl alcohol, but only sparingly soluble in boiling ethyl alcohol.

When a cold aqueous solution of the dibromide was added to a similar solution of sodium picrate in excess, an immediate precipitation of the *dipicrate* occurred. This salt, when collected, washed, and recrystallised from water, formed yellow crystals, m. p. 236—238° (Found : C, 37·7; H, 3·3; N, 10·6. $C_{24}H_{24}O_{14}N_6As_2$ requires C, 37·4; H, 3·1; N, 10·9%).

1 : 1 : 5 : *5-Tetramethyl-*o*-phenylenetrimethylene-diarsonium Dibromide* (1 : 1 : 4 : *4-Tetramethyl-*1 : *4-diarsonia-*2 : *3-benz*cyclo*hept-2-ene Dibromide*) (VIII).—This compound was prepared similarly to the previous dibromide, from the diarsine (6·1 g.) and trimethylene dibromide (2·15 c.c., 1 mol.) at 156—160°. Formation of a solid product first became apparent when the bath-temperature reached 135°. The *dibromide*, after recrystallisation from methyl alcohol, formed colourless hygroscopic crystals, m. p. 258° (effervescence) (Found : C, 32·0; H, 4·5; ionic Br, 32·6. $C_{13}H_{22}Br_2As_2$ requires C, 32·0; H, 4·5; ionic Br, 32·8%). This dibromide is freely soluble in cold water, but only very slightly soluble in boiling ethyl alcohol. A mixture of this compound and the dibromide (VI) had m. p. 248° (effervescence).

The corresponding *dipicrate*, prepared as before from a cold aqueous solution of the dibromide differed from the previous dipicrate in that it was almost insoluble in boiling water, methyl and ethyl alcohols. It was therefore collected, washed with water, and dried, and thus obtained as a yellow powder, m. p. 260° (Found: C, 38·5; H, 3·5; N, 10·7. $C_{25}H_{26}O_{14}N_6As_2$ requires C, 38·25; H, 3·3; N, 10·7%).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 24th*, 1949.]

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135. *Organo-lead Compounds. Part III.* N-*Trialkylplumbisulphonamides.*

By B. C. SAUNDERS.

A large variety of lead compounds of a new type, $RSO_2{\cdot}NR'{\cdot}PbR''_3$, has been prepared by two methods. They are highly crystalline, stable, compounds and all possess powerful sternutatory properties; many of them are intolerable at a concentration of 1 : 10^7. They are, therefore, more potent than the simpler trialkyl-lead salts already described in this series of papers. The most effective are *N-tri-*n*-propylplumbimethane-* and *tri-*n*-propylplumbibenzene-sulphonamide.*

IN 1940 McCombie and Saunders reported to the Ministry of Supply a new type of compound, namely, N-*triethylplumbitoluene*-p-*sulphonamide*, $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3$ (I), a colourless, stable, crystalline compound, recrystallisable from benzene and several other non-polar solvents. We prepared it in 73% yield by heating the sodio-derivative of toluene-*p*-sulphonamide with triethyl-lead chloride in alcohol:

$$C_6H_4Me{\cdot}SO_2{\cdot}NH\boxed{Na + Cl}PbEt_3 \rightarrow \underset{(I.)}{C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3} + NaCl$$

The compound had the lead content required for the formula (I) and was decomposed by passage of gaseous hydrogen chloride into its suspension in ether, giving pure toluene-*p*-sulphonamide and diethyl-lead dichloride. The latter was almost certainly a secondary product, the primary product being triethyl-lead chloride which is known to give the dichloride when its dilute ethereal solution is kept in the presence of excess of hydrogen chloride. Cleavage of (I) is therefore expressed as:

$$C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3 + HCl \longrightarrow C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + PbEt_3Cl$$

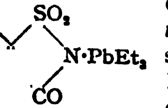
Examined as a sternutator by spraying its alcoholic solution, the sulphonamide (I) proved to be the most effective lead sternutator tested till then, being considerably more potent than the trialkyl-lead salts described in Parts I and II (*J.*, 1949, 919, 2983). It was intolerable at a concentration of 1 : 10^7. Similar syntheses gave N-*triethylplumbibenzenesulphonamide*, *tri-*n*-propylplumbitoluene-*p*-sulphonamide*, *and tri-*n*-propylplumbibenzenesulphonamide*, all stable crystalline compounds and, as expected, the introduction of the tri-*n*-propyl grouping increased the sternutatory action (see Part I, *loc. cit.*). For example, tri-*n*-propylplumbibenzenesulphonamide was a particularly powerful sternutator and at a concentration of 1 : 10^7 all the observers were forced to leave the testing-chamber after an exposure of only 40 seconds (sternutatory grade, 3; cf. Part I). In addition to its action on the nose, throat, chest, and gums, the compound produced irritation on the fingers and faces of some of the workers who undertook its preparation, particularly on a large scale.

In efforts to simplify the preparation it was found (1941) that mixing cold alcoholic solutions of tri-*n*-propyl-lead hydroxide and benzenesulphonamide and then adding water precipitated *N*-tri-*n*-propylplumbibenzenesulphonamide, practically pure even before recrystallisation, and in almost quantitative yield:

$$PbPr_3{\cdot}OH + C_6H_5{\cdot}SO_2{\cdot}NH_2 = C_6H_5{\cdot}SO_2{\cdot}NH{\cdot}PbPr_3 + H_2O$$

This method had wide application and gave excellent yields, particularly when the sulphonamide was markedly "acidic."

A variety of compounds of the type $R{\cdot}SO_2{\cdot}NR'{\cdot}PbR''_3$ was then prepared in which R = Me, Ph, *o*-C_6H_4Me, *p*-C_6H_4Me, or *p*-$NH_2{\cdot}C_6H_4$, R′ = H, Ph, *p*-C_6H_4Cl, or *p*-C_6H_4Br, and R″ = Et or Pr^n. These were, without exception, powerful sternutators, the most effective being *tri-*n*-propylplumbimethanesulphonamide*, $Me{\cdot}SO_2{\cdot}NH{\cdot}PbPr_3$, which was extremely unpleasant at a concentration of 1 : 2·5 × 10^7 (sternutatory grade 3^+). In addition, its lower molecular weight and high solubility in alcohol and other organic solvents increased its applicability.



(III.)

Saccharin reacted readily in cold alcohol with triethyl-lead hydroxide, giving *o-sulphobenzoic triethylplumbi-imide* (III). This and the corresponding *tri*-n-*propyl* derivative, like the acylic sulphonamides, were powerful sternutators, being intolerable at a concentration of 1 : 10^7 after only 1½ minutes. Even at this high dilution a " sweet taste " was noticed by the observers.

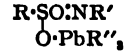
In Parts I and II we reported that an unsaturated grouping intensified the physiological action of an organo-lead compound. For example, triethyl-lead acrylate and tri-*n*-propyl-lead acrylate were more potent than the corresponding saturated salts. In view of the fact that the sulphonamide grouping also increases sternutatory action, it was decided to combine the two " active " groups in one molecule. We accordingly prepared N-*triethylplumbiethylenesulphonanilide*, $CH_2{=}CH{\cdot}SO_2{\cdot}NPh{\cdot}PbEt_3$, by the action of triethyl-lead chloride on the *sodio*-derivative of ethylenesulphonanilide. This sodium salt was soluble in alcohol and reacted smoothly. In this instance a purer product was obtained than when triethyl-lead hydroxide and the free ethylene sulphonanilide were used, as the latter anilide did not appear to be sufficiently acidic to react completely with the hydroxide. Although *N*-triethylplumbiethylenesulphonanilide gave an almost intolerable atmosphere at a concentration of 1 : 10^7, it did not show the expected increased potency compared with the simpler compounds.

As an example of a compound containing two $-SO_2{\cdot}NR{\cdot}PbR'_3$ groupings in the molecule, we prepared *methanedi-*(N-*triethylplumbisulphonanilide*) (IV), a powerful sternutator, but not exhibiting outstanding properties.

It should be pointed out that no definite chemical evidence has been produced to decide between formulæ (V) and (VI) for these compounds. Both would account for the cleavage by

$CH_2(SO_2{\cdot}NPh{\cdot}PbEt_3)_2$
(IV.)

$R{\cdot}SO_2{\cdot}NR'{\cdot}PbR''_3$
(V.)



$$\begin{array}{l}R{\cdot}SO{:}NR' \\ \;\;\;|\\ \;\;\;O{\cdot}PbR''_3\end{array}$$

(VI.)

hydrogen chloride into the parent sulphonamide and the trialkyl-lead chloride. The point could be decided by *X*-ray analysis, and it is hoped that this will be undertaken in the near future.

EXPERIMENTAL.

N-*Triethylplumbitoluene*-p-*sulphonamide*.—Toluene-*p*-sulphonamide (3·4 g.) was dissolved in alcohol, and sodium (0·5 g.) was added. The white flaky precipitate produced was filtered off, washed with alcohol, and dried. To this sodio-derivative (1·93 g.), suspended in alcohol, triethyl-lead chloride (3·3 g.) was added and the whole heated under reflux for 20 minutes. The product was then cooled and filtered, and to the filtrate water was added until the solid *triethylplumbitoluene*-p-*sulphonamide* crystallised out. After being washed with water, dried, and recrystallised from benzene, it had m. p. 127° (Found: Pb, 44·53. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

Cleavage by hydrogen chloride. (*a*) Triethylplumbitoluene-*p*-sulphonamide was suspended in a *large* volume of ether, and dry hydrogen chloride passed in. The substance dissolved and, after saturation, the solution was set aside. Diethyl-lead dichloride separated (Found : Pb, 62·2. Calc. for $C_4H_{10}Cl_2Pb$: Pb, 61·9%).

(*b*) Triethylplumbitoluene-*p*-sulphonamide was suspended in the *minimum* volume of ether and treated as in (*a*). A lead-free solid separated rapidly and had m. p. 138°. It was shown to be toluene-*p*-sulphonamide.

N-*Triethylplumbibenzenesulphonamide*.—Prepared as above, but by use of molecular quantities of sodiobenzenesulphonamide and triethyl-lead chloride, and recrystallised from benzene, the *sulphonamide* had m. p. 132° (Found : Pb, 45·9. $C_{12}H_{21}O_2NSPb$ requires Pb, 46·0%).

N-*Tri*-n-*propylplumbitoluene*-p-*sulphonamide*.—Sodiotoluene-*p*-sulphonamide (3·6 g.) was suspended in alcohol and tri-*n*-propyl-lead chloride (6·5 g.) was added. Subsequent treatment as above, and recrystallisation from light petroleum (b. p. 80—100°) gave the *amide*, m. p. 100—101° (Found : Pb, 41·1. $C_{16}H_{29}O_2NSPb$ requires Pb, 40·9%).

N-*Tri*-n-*propylplumbibenzenesulphonamide*.—(*a*) Prepared and purified as in the preceding paragraph, N-*tri*-n-*propylplumbibenzenesulphonamide* (73%, crude) had m. p. 96° (Found: Pb, 41·6. $C_{15}H_{27}O_2NSPb$ requires Pb, 42·1%).

(*b*) To an alcoholic solution of tri-*n*-propyl-lead hydroxide (from 3·7 g. of the chloride) was added an alcoholic solution of benzenesulphonamide (1·6 g.). Water was added, and after 10 minutes the product was filtered off. 118 G. of crude but almost pure material were recrystallised, yielding 101 g. of the pure sulphonamide, m. p. 93·5—94·5°. 5 C.c. of alcohol dissolved 3·2 g. of the sulphonamide at 15°, and after 6 days the substance was reprecipitated unchanged (m. p. 93·5—94·5°) by the addition of water.

Tripropylplumbitoluene-*p*-sulphonamide, triethylplumbibenzenesulphonamide, and triethylplumbitoluene-*p*-sulphonamide were also prepared by method (*b*), from the calculated quantities of hydroxide and sulphonamide.

N-*Triethylplumbimethanesulphonamide*.—Methanesulphonamide (0·95 g.) was dissolved in hot benzene and mixed with triethyl-lead hydroxide (3·11 g.) dissolved in benzene. The mixture was heated under reflux for 30 minutes on a water-bath. After cooling, a very small quantity of a solid separated and was recrystallised from aqueous alcohol; this decomposed at 197° (Found: Pb, 56·2%). To the filtrate light petroleum was added to precipitate the white crystalline *triethylplumbimethanesulphonamide* which, recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 97° (Found: Pb, 53·4. $C_7H_{19}O_2NSPb$ requires Pb, 53·4%).

N-*Tri*-n-*propylplumbimethanesulphonamide*.—Freshly prepared moist silver oxide (2·8 g.) was suspended in benzene and a small quantity of alcohol added. To this was added tripropyl-lead chloride (3·7 g.) dissolved in benzene, and the mixture shaken and then filtered. The filtrate was added to methanesulphonamide (0·95 g.) dissolved in hot benzene, and the procedure of the previous experiment then followed. The *amide* had m. p. 67° (Found: Pb, 48·1. $C_{10}H_{25}O_2NSPb$ requires Pb, 48·2%).

N-*Triethylplumbimethanesulphonanilide*.—Benzene solutions of methanesulphonyl chloride (3·42 g.) and aniline (5·52 g.) were mixed. After 20 minutes, light petroleum (b. p. 40—60°) was added, and the precipitated mixture of aniline hydrochloride and methanesulphonanilide was boiled with benzene and filtered. To the benzene filtrate, light petroleum was added. Methanesulphonanilide, m. p. 100°, separated (Found: C, 49·5; H, 5·6. Calc. for $C_7H_9O_2NS$: C, 49·1; H, 5·3%). The methanesulphonanilide (0·85 g.), dissolved in alcohol, was added to triethyl-lead hydroxide (1·55 g.) and set aside for 30 minutes. The white crystalline *triethylplumbimethanesulphonanilide* which separated on the addition of water was recrystallised from benzene–light petroleum (b. p. 40—60°), and had m. p. 115·5° (Found: Pb, 44·1. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

N-*Triethylplumbisulphanilamide*.—A solution of sulphanilamide (1·72 g.) in alcohol was added to a solution of triethyl-lead hydroxide (3·12 g.) in alcohol. After 30 minutes the mixture was filtered, and to the filtrate water was added. The colourless *triethylplumbisulphanilamide* which separated was recrystallised from alcohol and then had m. p. 171° (Found: Pb, 43·9. $C_{12}H_{22}O_2N_2SPb$ requires Pb, 44·55%).

N-*Tri*-n-*propylplumbisulphanilamide*.—Prepared similarly, the alcoholic solution of the hydroxide being made by shaking the chloride (3·7 g.) in alcohol with moist silver oxide (2·8 g.) for 10 minutes before filtration, *tri*-n-*propylplumbisulphanilamide* had m. p. 101° after recrystallisation from benzene (Found: Pb, 40·9. $C_{15}H_{28}O_2N_2SPb$ requires Pb, 40·9%).

o-*Sulphobenzoic Triethylplumbi-imide*.—A solution of triethyl-lead hydroxide (3·11 g.) in alcohol was added to an alcoholic solution of saccharin (1·8 g.). After 30 minutes the mixture was cooled in ice-water, and water added until a turbidity was produced. On scratching of the vessel, a white solid separated which was recrystallised from a mixture of benzene and light petroleum (b. p. 60—80°). The *lead* derivative was thus obtained as colourless needles, m. p. 135°, containing nitrogen and sulphur (Found: Pb, 44·4. $C_{13}H_{19}O_3NSPb$ requires Pb, 44·1%).

The compound was dissolved in ether and dry hydrogen chloride passed in. Crystals of saccharin separated and, on storage, diethyl-lead dichloride gradually separated from the filtrate.

o-*Sulphobenzoic Tri*-n-*propylplumbi-imide*.—Prepared from alcoholic solutions of tripropyl-lead hydroxide (from the chloride) and saccharin, and recrystallised from benzene–light petroleum (b. p. 60—80°), the *imide* had m. p. 130° (Found: Pb, 39·4. $C_{16}H_{25}O_3NSPb$ requires Pb, 40·0%).

N-*Triethylplumbitoluene*-p-*sulphonanilide*.—Prepared from the sulphonanilide (2·51 g.) and triethyl-lead hydroxide (3·12 g.) in alcohol, and recrystallised from aqueous alcohol, the *sulphonanilide* had m. p. 134° (Found: Pb, 37·8. $C_{19}H_{27}O_2NSPb$ requires Pb, 38·35%).

N-*Tri*-n-*propylplumbitoluene*-p-*sulphonanilide*.—Prepared similarly to the corresponding sulphanilamide, from the chloride (3·7 g.) and the sulphonanilide (2·51 g.), and recrystallised from aqueous alcohol, this *anilide* had m. p. 104° (Found: Pb, 35·0. $C_{22}H_{33}O_2NSPb$ requires Pb, 35·6%).

N-*Triethylplumbitoluene*-o-*sulphonamide*.—Prepared from toluene-*o*-sulphonamide and triethyl-lead hydroxide, and recrystallised from aqueous alcohol, the *amide* had m. p. 133° (Found: Pb, 44·6. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

N-*Triethylplumbitoluene*-p-*sulphon*-p′-*chloroanilide*.—Prepared from alcoholic solutions of toluene-*p*-sulphon-*p′*-chloroanilide and triethyl-lead hydroxide, the *lead* derivative was recrystallised from benzene and light petroleum, and had m. p. 111·5° (Found: Pb, 36·05. $C_{19}H_{26}O_2SNClPb$ requires Pb, 36·1%).

N-*Tri*-n-*propylplumbitoluene*-p-*sulphon*-p′-*chloroanilide*, m. p. 123° (Found: Pb, 33·5. $C_{22}H_{32}O_2NSClPb$ requires Pb, 33·6%), and *triethylplumbitoluene*-p-*sulphon*-p′-*bromoanilide*, m. p. 117° (from benzene) (Found: Pb, 33·15. $C_{19}H_{26}O_2NSBrPb$ requires Pb, 33·48%), were similarly prepared.

Sodium Ethane-1 : 2-*disulphonate* (cf. *Annalen*, 1886, **148**, 96, and *J.*, 1922, 120).—The calculated quantities of ethylene dibromide and sodium sulphite ($7H_2O$) were heated under reflux with the minimum amount of water needed to dissolve the sulphite. After 3 hours, the mixture was evaporated to crystallisation, and the solid obtained was dried at 120°. Yield, 75%.

Ethanedisulphonyl Chloride.—To the crude sodium salt, phosphorus pentachloride (2 mols.) was added, and the reaction completed by careful warming. The phosphorus oxychloride was distilled off at 15 mm. and the residue ground with ice and extracted with ether. The ethereal extract was dried (Na_2SO_4) and evaporated. The product, recrystallised from light petroleum (b. p. 100—110°), had m. p. 91° (yield 55%).

Ethylenesulphonanilide.—The above sulphonyl chloride (25 g.) was dissolved in ether (30 c.c.), and aniline (31 g.), also in ether (20 c.c.), was added. (If excess of aniline was used, side-reactions took place.) Heat was evolved, and when the addition was complete the mixture was boiled until no more sulphur dioxide was evolved. The precipitated aniline hydrochloride was filtered off and washed with ether. The ethereal solutions were extracted with hydrochloric acid and dried (Na_2SO_4), the ether was distilled off, and the residue recrystallised from alcohol; it had m. p. 69° (yield 55%).

Sodioethylenesulphonanilide.—Ethylenesulphonanilide (11 g.) was dissolved in aqueous sodium hydroxide solution (25 c.c.; 10%) by warming. The solution was filtered and cooled in ice, and the crystalline precipitate which formed was filtered off and dried on a porous plate. This product was washed with ether, again filtered, and dried *in vacuo* over concentrated sulphuric acid.

The crude product was readily soluble in alcohol, but was recrystallised by adding a small quantity of light petroleum (b. p. 60—80°) to a hot alcoholic solution, filtering this solution while hot and then cooling it in ice. The crystalline *sodioethylenesulphonanilide* was dried *in vacuo* over calcium chloride.

The yield of pure product was 2 g. (16%) (Found: C, 46·6; H, 3·9; N, 7·1. $C_8H_8O_2NSNa$ requires C, 46·8; H, 3·9; N, 7·5%). The compound was readily soluble in water or alcohol, slightly soluble in acetone, and insoluble in ether, chloroform, or benzene. When the compound was heated slowly the m. p. was sharp (69°; this is the m. p. of the original ethylenesulphonanilide). On further heating of the sodio-derivative, fusion was followed by decomposition and charring, and finally a white residue of sodium sulphate remained.

An aqueous solution, on acidification with dilute sulphuric acid, gave a white precipitate of the original sulphonanilide (m. p. 69°).

N-*Triethylplumbiethylenesulphonanilide*.—Triethyl-lead chloride (1·2 g.) in alcohol (10 c.c.) and sodioethylenesulphonanilide (0·75 g.) in alcohol (10 c.c.) were mixed and kept at room temperature for 15 hours. Sodium chloride (0·2 g., theoretical yield) was filtered off, and the filtrate poured into water. The white precipitate which separated was filtered off, washed with water, and dried *in vacuo*. The crude *lead* derivative recrystallised as colourless leaflets from light petroleum (b. p. 100—120°) (Found: N, 3·0. $C_{14}H_{23}O_2NSPb$ requires N, 2·95%) (yield 1 g., 55%). When heated gradually, it melted sharply at 116°. When heated in the open in bulk it decomposed with a mild explosion.

Methanedisulphonyl Chloride.—Methanedisulphonic acid was prepared from acetylene and fuming sulphuric acid by the method of Schroeter (*Annalen*, 1919, **418**, 183). To the dehydrated acid (20 g.), phosphorus pentachloride (48 g.) was added in small quantities. When the addition was complete, the mixture was heated on a water-bath for 15 minutes and then the phosphorus oxychloride was distilled off at 42°/20 mm. The residue on distillation at 143°/20 mm. gave the pure disulphonyl chloride (20 g., 83%).

Methanedisulphonanilide.—Aniline (9·3 g.) in benzene (50 c.c.) was added to methanedisulphonyl chloride (5·3 g.) in benzene (35 c.c.). The mixture was boiled under reflux for 10 minutes, cooled, shaken with sodium hydroxide (4 g.) in water (25 c.c.), and filtered through sintered glass to remove a slight precipitate. The aqueous layer was separated, extracted with more benzene, and then acidified with dilute hydrochloric acid. The precipitate was purified by repeated dissolution in dilute sodium hydroxide solution, washing with benzene, and reacidification. The disulphonanilide thus obtained (3·8 g., 50%) was dried *in vacuo* over solid potassium hydroxide and paraffin wax.

Methanedi-(N-*triethylplumbisulphonanilide*).—Triethyl-lead hydroxide (2 g.) was added to methanedisulphonanilide (1 g.) in a mixture of water (10 c.c.) and alcohol (10 c.c.), and heated till clear. The solution was filtered while hot, and on cooling colourless crystals were obtained and recrystallised from aqueous alcohol. *Methane di*-(N-*triethylplumbisulphonanilide*) was obtained as long colourless needles, insoluble in water, soluble in alcohol and in hot benzene. The compound did not melt, but sintered at 71° and decomposed at 180° with effervescence. For lead analysis (see Part I, *loc. cit.*) the compound was first decomposed by nitric acid in a sealed tube (Found: Pb, 44·9. $C_{25}H_{42}O_4N_2S_2Pb_2$ requires Pb, 45·4%).

The author thanks the Chief Scientific Officer of the Ministry of Supply for permission to publish this work, and is also indebted to the following for considerable help with some of the preparative work: R. Heap, F. E. Smith, and G. J. Stacey.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 24th*, 1949.]

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136. *Steroids and the Walden Inversion. Part VI. Reduction of Cholest-5-en-3-one with Lithium Aluminium Hydride.*

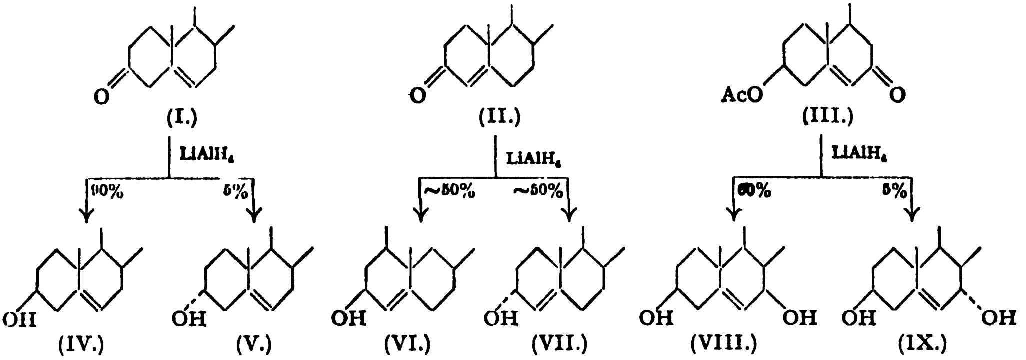
By C. W. SHOPPEE and G. H. R. SUMMERS.

Cholest-5-en-3-one by reduction with lithium aluminium hydride gives unexpectedly much cholesterol and very little *epi*cholesterol; the stereochemical course of the reduction is compared with that of other steroid ketones.

LITHIUM ALUMINIUM HYDRIDE (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199) is a valuable reagent for reduction of variants of the carboxyl group: R—CO—X ⟶ R·CH$_2$·OH (X = H, OH, OR′, Cl) (Nystrom and Brown, *ibid.*, pp. 1197, 1548). Further, ketones give secondary alcohols, whilst amides yield primary amines (Uffer and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397), but simple ethylenic linkages are unaffected.

Reduction of cholest-5-en-3-one (I) without alteration of the position of the double bond can be carried out only in neutral media, since this compound is readily isomerised, *e.g.*, by simple filtration in pentane solution through non-neutralised aluminium oxide, to cholest-4-en-3-one (II). Partial hydrogenation of (I) with Raney nickel in *cyclo*hexane yields considerable but variable quantities of *epi*cholesterol (V) (Ruzicka and Goldberg, *Helv. Chim. Acta*, 1936, **19**, 1407); since reduction with lithium aluminium hydride has been observed sometimes to offer advantages over catalytic hydrogenation (cf. Plattner *et al.*, *ibid.*, 1949, **32**, 265; Salamon, *ibid.*, p. 1306), we have used this reagent to reduce (I). Reduction proceeds smoothly to give cholesterol (IV) and *epi*cholesterol (V) but the yield of the latter is only about 5%.

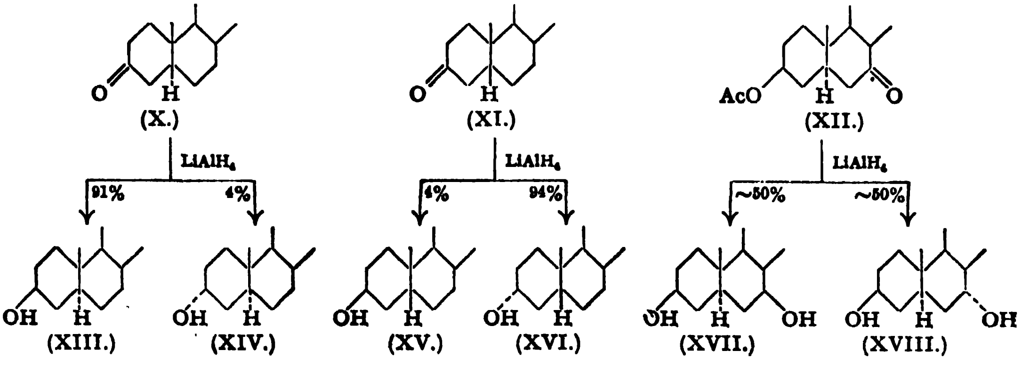
The one-sided stereochemical course in the reduction of (I) is surprising since similar reduction of cholest-4-en-3-one (II) leads to approximately equal quantities of the epimeric cholest-4-en-3-ols * (McKennis, jun., and Gaffney, *J. Biol. Chem.*, 1948, **175**, 217); this result has been confirmed by Plattner *et al.*, (*loc. cit.*). On the other hand, it has recently been reported that reduction of 7-ketocholesteryl acetate (III) with lithium aluminium hydride proceeds largely in one stereochemical direction to give mainly cholest-5-ene-3β : 7β-diol (VIII) accompanied by 5% of cholest-5-ene-3β : 7α-diol (IX) (Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, 71, 2226).



In reduction by lithium aluminium hydride the active entity appears to be the anion $AlH_4^{\ominus}$ and, since in the reductive fission of epoxides attack at carbon is accompanied by inversion of configuration, it has been suggested that the reaction is a bimolecular nucleophilic replacement, S_N2 (Trevor and Brown, *ibid.*, p. 1675). Reduction of a carbonyl group is a bimolecular addition reaction, so that steric factors should operate (cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173).

Although the presence in (I), (II), and (III) of a double bond at the bridgehead ensures that the lower portions of rings A and B are essentially flat, steric hindrance by the angular methyl group at $C_{(10)}$, arising from repulsion by the electrons of the three C–H bonds, might impede frontal as compared with rearward attack at $C_{(3)}$ by the anion $AlH_4^{\ominus}$. Such hindrance would be consistent with the predominance of the 3β-hydroxy-epimeride (IV) and the 7β-hydroxy-epimeride (VIII), but would be expected also to lead to production of (VI) as the major epimeride.

We have also examined the reduction by lithium aluminium hydride of cholestan-3-one (X) and coprostan-3-one (XI); the former gives cholestanol (XIII) with ~4% of *epi*cholestanol (XIV), whilst the latter yields *epi*coprostanol (XVI) accompanied by ~4% of coprostanol (XV). These results closely resemble those obtained by catalytic hydrogenation in neutral media (Diels and Abderhalden, *Ber.*, 1906, 39, 884; Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, 17, 1407). The production of (XIII) as principal product is consistent with lesser hindrance at $C_{(3)}$ by the angular methyl group at $C_{(10)}$; in the favoured formation of (XVI) this is not the case, unless the numerous constellations accessible to rings A and B in derivatives of coprostane (Shoppee, *Ann. Reports*, 1946, 43, 200) combine effectively to eliminate steric hindrance by the angular methyl group at $C_{(3)}$. If hindrance by the hydrogen atom at $C_{(5)}$ is envisaged, as in discussion of the differential rates of alkaline hydrolysis [S_N2] of the 3-acyl derivatives of the alcohols (XIII—XVI) (Ruzicka, Furter, and Goldberg, *Helv. Chim. Acta*, 1938, 21, 498), then frontal attack by the anion $AlH_4^{\ominus}$ at $C_{(3)}$ in (X), and similar but rearward attack in (XI), should be the less hindered, leading



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* Formerly called "allocholesterol" and "*epi*allocholesterol."

respectively to predominant production of (XIV) not (XIII), and (XV) not (XVI). From both points of view it is curious that in the cholestane series, where ring B is certainly a rigid chair-form, it has been found that reduction of 7-ketocholestanyl acetate (XII) with lithium aluminium hydride gives approximately equal quantities of cholestane-3β : 7β-diol (XVII) and of the 3β : 7α-diol (XVIII) (Fieser, Fieser, and Chakravarti, *loc. cit.*; cf. Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503).

Finally, it may be remarked that asymmetric induction at $C_{(3)}$ by the other six nuclear asymmetric centres might be expected to produce a considerable effect because they occupy fixed positions, relative to $C_{(3)}$, in a polycyclic system; for the same reason variation of such an effect in opposite senses would not be expected.

EXPERIMENTAL.

(M. p.s were determined thermo-electrically on a Kofler block, and are therefore corrected; limit of error ±2°. All solvents were rigorously purified and dried.)

Cholest-5-en-3-one (I).—This was prepared by the method of Butenandt and Schmidt-Thomé (*Ber.*, 1936, **69**, 882; cf. Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244); the crude product, m. p. 120—124°, is readily purified by dissolution in pentane, filtration of the solution through a column of neutralised aluminium oxide * (activity II—III, 30 × wt. of the crude product) prepared in pentane, and subsequent washing with pentane. The material so eluted, by a single recrystallisation from acetone or ethanol, gave the ketone as needles, m. p. 127°.

Reduction with lithium aluminium hydride. To a vigorously stirred solution of lithium aluminium hydride (2·17 g.) in ether (150 c.c.) cholest-5-en-3-one (I) (m. p. 127°; 2·56 g.), dissolved in ether (100 c.c.), was added during 25 minutes. The mixture was stirred for 2 hours with addition of ether from time to time, the solution becoming opaque; thereafter the reaction-flask was cooled in ice, and excess of lithium aluminium hydride destroyed with ice-cold 0·1N-sulphuric acid. The ethereal layer was separated, the acidic solution extracted twice with ether, and the combined ethereal solutions washed with water, sodium hydrogen carbonate solution, and again with water, dried (Na_2SO_4), and evaporated to give a white solid (2·56 g.; m. p. 133—138°). A portion (326 mg.) of the reduction product, dissolved in ethanol (50 c.c.), was treated with a warm 1% solution of digitonin in 95% ethanol (200 c.c.). After being kept overnight, the precipitate of cholesterol digitonide was filtered off and dried (1·2363 g., ≡ 295 mg. of cholesterol); decomposition of the digitonide by dissolution in pyridine (15 c.c.) and precipitation of digitonin with ether (200 c.c.), followed by working up of the resulting filtrate, gave cholesterol (290 mg.), m. p. 148° after crystallisation from ethanol. The original alcoholic filtrate was evaporated completely in a vacuum, and the residue repeatedly extracted with ether; the combined ethereal extracts, after being washed with 2N-hydrochloric acid, water, sodium hydrogen carbonate solution, and water, were dried (Na_2SO_4) and evaporated to yield an oil which solidified on cooling. Crystallisation from aqueous ethanol gave *epi*cholesterol (12 mg.) as plates, m. p. 140°, mixed m. p. 140—141°. The proportion of cholesterol in the reduction product was thus 90·5%.

Conversion into Cholest-4-en-3-one (II). Cholest-5-en-3-one (m. p. 127°; 320 mg.), dissolved in pentane (30 c.c.), was filtered through a column of aluminium oxide (Spence type H, activity II, 10 g.) prepared in pentane. Evaporation of the filtrate gave crystalline material (m. p. 80—81° after slight softening; 102 mg.); elution with pentane, with benzene–pentane mixtures, and with benzene gave various fractions (m. p. 73° to 80°; 215 mg.). All fractions were united and recrystallised from ether–methanol to give cholest-4-en-3-one (III), m. p. 80—81°, undepressed by admixture with an authentic specimen.

Reduction of Cholestan-3-one (X) *with Lithium Aluminium Hydride.*—The procedure was that described for cholest-5-en-3-one (I). Cholestan-3-one (m. p. 129—130°; 884 mg.) gave a reduction product (890 mg.); a portion (350 mg.), dissolved in ethanol (100 c.c.), was treated with a warm 1·33% solution of digitonin in 95% ethanol (150 c.c.). The insoluble digitonide was filtered off and gave by appropriate treatment cholestan-3β-ol (319 mg.), double m. p. 125° and 140—141° after crystallisation from methanol. The alcoholic filtrate by evaporation and ether-extraction of the residue yielded cholestan-3α-ol (12 mg.), m. p. 180—181° after crystallisation from aqueous methanol. The proportion of cholestan-3β-ol in the reduction product was thus 91%.

Reduction of Coprostan-3-one (XI) *with Lithium Aluminium Hydride.*—The procedure was that described above; coprostan-3-one (m. p. 59—61°; 950 mg.) gave a reduction product (948 mg.), a portion of which (318 mg.) was separated by treatment with digitonin as above. Only a small precipitate was obtained after storage overnight; this by appropriate treatment gave material (18 mg.) which after crystallisation from methanol yielded coprostan-3β-ol as needles, m. p. 100°, undepressed by admixture with a genuine specimen. Evaporation of the alcoholic filtrate and ether-extraction of the residue furnished crystals (m. p. 102—106° crude); recrystallisation from acetone gave coprostan-3α-ol (300 mg.), m. p. 115—116°, alone or mixed with an authentic specimen. The proportion of coprostan-3-α-ol in the reduction product was thus 94%.

One of us (C. W. S.) acknowledges gratefully a grant from the Royal Society which has partly defrayed the expense of this work, whilst the other (G. H. R. S.) acknowledges the award of a Postgraduate Studentship by the University of Wales and a grant from the Department of Scientific and Industrial Research which enabled him to participate in this investigation.

UNIVERSITY COLLEGE, SWANSEA, THE UNIVERSITY OF WALES. [*Received, December 7th*, 1949.]

* Prepared by washing with warm aqueous sodium hydroxide and then warm acetic acid and then washed to neutrality with water; reactivated at 200° for 30 hours.

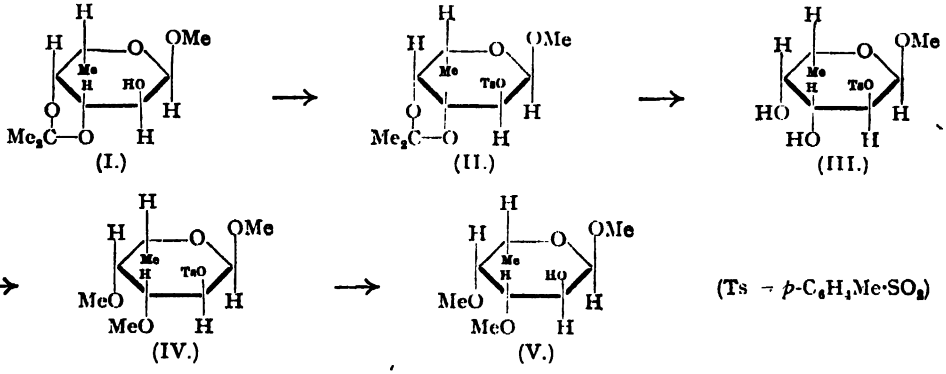
137. 3 : 4-*Dimethyl* L-*Fucose and* 2 : 3-*Dimethyl* L-*Rhamnose.*

By E. E. Percival and E. G. V. Percival.

From 2-*toluene*-p-*sulphonyl* 3 : 4-iso*propylidene α-methyl*-L-*fucoside* by mild hydrolysis, methylation, and reduction, 3 : 4-*dimethyl α-methyl*-L-*fucoside* and 3 : 4-*dimethyl* L-*fucose* have been prepared. 2 : 3-Dimethyl L-rhamnose has been prepared by a similar route.

The isolation of a dimethyl L-fucose from methylated fucoidin made it desirable to prepare synthetic dimethyl fucoses of known structure. The preparation and properties of the 3 : 4-dimethyl isomer are now recorded.

α-Methyl-L-fucoside was converted into the 3 : 4-*iso*propylidene derivative (I) (MacPhillamy and Elderfield, *J. Org. Chem.*, 1939, **4**, 150) from which 2-*toluene*-p-*sulphonyl* 3 : 4-iso*propylidene α-methyl*-L-*fucoside* (II) was prepared. Methanolysis removed the acetone residue (to give III), and methylation then gave 2-*toluene*-p-*sulphonyl* 3 : 4-*dimethyl α-methyl*-L-*fucoside* (IV). Reductive fission of the toluene-*p*-sulphonyl residue gave 3 : 4-*dimethyl α-methyl*-L-*fucoside* (V) from which by hydrolysis 3 : 4-*dimethyl* L-*fucose* was obtained as the monohydrate, m. p. 75°, $[\alpha]_D$ −118°.



(I.) (II.) (III.) (IV.) (V.)

(Ts = p-$C_6H_4Me{\cdot}SO_2$)

By a similar process 2 : 3-*iso*propylidene α-methyl-L-rhamnoside was converted into 4-*toluene*-p-*sulphonyl* 2 : 3-*dimethyl α-methyl*-L-*rhamnoside* from which, by reductive hydrolysis followed by the removal of the glycosidic methyl group, 2 : 3-dimethyl L-rhamnose was prepared as a syrup, $[\alpha]_D$ +40°. This compound prepared by another route (Schmidt, Plankenhorn, and Kübler, *Ber.*, 1942, **75**, 579) is reported to have $[\alpha]_D$ +47·6°. Crystalline 2 : 3-*dimethyl* L-*rhamnose anilide* has been prepared.

By the paper chromatogram the R_G values (Hirst, Hough, and Jones, *J.*, 1949, 928) of both dimethyl 6-deoxyhexoses have been determined and compared with those of 2-methyl fucose and 4-methyl rhamnose, prepared by the methylation and hydrolysis of the corresponding *iso*propylidene α-methylglycosides. Certain differences between the results obtained and those

Sugar.	R_G.	Sugar.	R_G.
4-Methyl L-rhamnose	0·64; 0·65 (0·57)	2-Methyl L-fucose	0·56 (0·51)
2 : 3-Dimethyl L-rhamnose ...	0·82; 0·83	3 : 4-Dimethyl L-fucose	0·67; 0·68

previously published (Hirst, Hough, and Jones, *loc. cit.*) (in parentheses) emphasise the point made in that publication that such figures are useful as an indication of the methylated sugar concerned, but that direct comparisons on the same chromatogram are essential before identity (in the chromatographic sense) can be established, because of the difficulty of the rigid standardisation of all the variables between different laboratories.

Experimental.

3 : 4-iso*Propylidene α-Methyl*-L-*fucoside.*—α-Methyl-L-fucoside (1 g.) in acetone (50 c.c.) containing two drops of acetaldehyde was shaken with anhydrous copper sulphate (11 g.) for 120 hours. One drop of concentrated sulphuric acid was then added, and shaking continued for a further 14 hours. After filtration and neutralisation with potassium carbonate, the solvent was evaporated; the product (0·9 g.), distilled at 95°/0·01 mm., had n_D^{15} 1·4621, $[\alpha]_D^{15}$ −160° (c, 1·0 in water). On storage in the refrigerator the product solidified.

2-*Toluene*-p-*sulphonyl* 3 : 4-iso*Propylidene α-Methyl*-L-*fucoside.*—The above derivative (0·51 g.) in pyridine (5 c.c.) was treated with powdered toluene-*p*-sulphonyl chloride (1 g.) and kept for 2 days at 15°.

When the mixture was poured on ice a white crystalline solid was obtained which was combined with the product obtained on extraction of the filtrate with chloroform, which was washed with dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. On recrystallisation from methanol a crystalline *product* (0·37 g.), m. p. 182°, $[\alpha]_{D}^{15}$ $-146°$ (*c*, 1·0 in $CHCl_3$), was obtained (Found: C, 54·7; H, 6·5; OMe, 8·5. $C_{17}H_{24}O_7S$ requires C, 54·8; H, 6·45; OMe, 8·3%).

2-Toluene-p-*sulphonyl* 3 : 4-*Dimethyl α-Methyl*-L-*fucoside*.—Crystalline 2-toluene-*p*-sulphonyl 3 : 4-*iso*propylidene α-methylfucoside (0·5 g.) was treated with methanolic hydrogen chloride (10 c.c.; 1%) at 70° for 1 hour. After neutralisation with silver carbonate and extraction of the silver residues with ethanol, 2-*toluene*-p-*sulphonyl α-methyl*-L-*fucoside* (0·36 g.), m. p. 158°, $[\alpha]_{D}^{15}$ $-85°$ (*c*, 1·0 in chloroform), was obtained. This substance was then methylated 4 times with methyl iodide and silver oxide, to give a crystalline *product* (0·4 g.) which, recrystallised from chloroform–light petroleum (b. p. 60—80°), had m. p. 103°, $[\alpha]_{D}^{15}$ $-84°$ (*c*, 0·7 in chloroform) (Found: C, 53·6; H, 6·8; OMe, 16·6; S, 8·2. $C_{16}H_{24}O_7S$ requires C, 53·3; H, 6·7; OMe, 17·2; S, 8·9%).

3 : 4-*Dimethyl α-Methyl*-L-*fucoside*.—The above compound (0·5 g.) in methanol (11 c.c.) and water (5 c.c.) was treated with sodium amalgam (10 g.; 4%) with stirring at 35° during 17 hours. After filtration and extraction with chloroform, the extracts were treated with carbon dioxide for 15 minutes, dried (Na_2SO_4), and freed from organic solvents under diminished pressure. The aqueous residue was neutralised with carbon dioxide, evaporated to dryness, and extracted with ether. From these operations a crystalline *fucoside* was obtained (0·2 g.) which was recrystallised from boiling light petroleum (b. p. 40—60°), to give crystals, m. p. 100°, $[\alpha]_{D}^{20}$ $-213°$ (*c*, 1·3 in water) (Found: C, 52·1; H, 8·5; OMe, 44·6. $C_9H_{18}O_5$ requires C, 52·4; H, 8·6; OMe, 45·1%).

3 : 4-*Dimethyl* L-*Fucose*.—3 : 4-Dimethyl α-methyl-L-fucoside (0·13 g.) was hydrolysed at 100° with sulphuric acid (15 c.c.; 4%) for 3 hours, whereafter the rotation was constant. After neutralisation with barium carbonate, evaporation to dryness, and extraction with acetone, a crystalline *ether* (0·1 g.) was obtained, having m. p. 82° (from ethanol), m. p. 76° (from chloroform–light petroleum), $[\alpha]_{D}^{15}$ $-118°$ (*c*, 1·1 in water) (Found: C, 45·9; H, 8·9; OMe, 27·9. $C_8H_{16}O_5,H_2O$ requires C, 45·6; H, 8·6; OMe, 29·5%).

4-*Toluene*-p-*sulphonyl* 2 : 3-iso*Propylidene α-Methyl*-L-*rhamnoside*.—Anhydrous rhamnose (12 g.) was boiled with methanolic hydrogen chloride (150 c.c.; 0·25%) until non-reducing (40 hours) and the syrupy α-methylrhamnoside ($[\alpha]_{D}$ $-48°$) isolated. Treatment with acetone as previously described gave a good yield of the *iso*propylidene derivative which distilled at 110°/0·05 mm., n_{D}^{11} 1·4563, $[\alpha]_{D}^{12}$ $-14°$ (*c*, 1·1 in acetone). Treatment of this product (3 g.) with toluene-*p*-sulphonyl chloride (5·5 g.) and pyridine (14 c.c.) as described above gave, on pouring of the mixture into ice-water, a crystalline substance which was recrystallised (2·7 g.) from methanol and had m. p. 60°, $[\alpha]_{D}^{15}$ $+22·5°$ (*c*, 2·9 in methanol) (cf. Levene and Compton, *J. Amer. Chem. Soc.*, 1935, **57**, 2306, who quote m. p. 61—62°, $[\alpha]_{D}$ $+22°$ in methanol).

4-*Toluene*-p-*sulphonyl* 2 : 3-*Dimethyl α-Methylrhamnoside*.—Removal of the *iso*propylidene residue as described above gave a syrupy *rhamnoside*, $[\alpha]_{D}$ $-73·5°$ (*c*, 1·4 in chloroform), n_{D}^{12} 1·5208 (Found: S, 8·9; OMe, 8·0. $C_{14}H_{20}O_7S$ requires S, 9·6; OMe, 9·3%). Methylation with methyl iodide and silver oxide in 3 operations gave a crystalline *ether* (1·9 g.) which, recrystallised from chloroform–light petroleum (b. p. 60—80°), had m. p. 111°, $[\alpha]_{D}$ $-33°$ (*c*, 2·0 in chloroform) (Found: C, 52·8; H, 6·4; OMe, 25·0. $C_{16}H_{24}O_7S$ requires C, 53·3; H, 6·7; OMe, 25·8%).

2 : 3-*Dimethyl α-Methylrhamnoside and* 2 : 3-*Dimethyl Rhamnose*.—Treatment of the above derivative (1 g.) with sodium amalgam as described previously gave 2 : 3-*dimethyl α-methylrhamnoside* as a syrup (0·5 g.) which distilled at 110°/0·05 mm. and had n_{D}^{16} 1·4538, $[\alpha]_{D}$ $-6°$ (*c*, 2·0 in water) (Found: OMe, 43·2. $C_9H_{18}O_5$ requires OMe, 45·1%). Hydrolysis with sulphuric acid (4%) was complete in 6 hours; 2 : 3-dimethyl rhamnose isolated as above had $[\alpha]_{D}$ $+40°$ (*c*, 0·7 in water) (Found: OMe, 30·0. Calc. for $C_8H_{16}O_5$: OMe, 32·3%). Treatment of the syrup (0·4 g.) in ethanol (5 c.c.) with aniline (0·4 g.) at 80° for 2 hours followed by evaporation at room temperature gave an *anilide*, m. p. 138—139° (Found: C, 62·3; H, 7·9; N, 4·9; OMe, 21·4. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2; OMe, 23·2%).

Periodate Oxidation [with A. G. Ross].—Estimation of the acetaldehyde liberated on oxidation with periodate (Cameron, Ross, and Percival, *J. Soc. Chem. Ind.*, 1948, **67**, 161) gave only 5·6% of the theoretical amount.

Thanks are expressed to Imperial Chemical Industries Limited for grants.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH.

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138. *A Theoretical Treatment of the Diels–Alder Reaction. Part I. Polycyclic Aromatic Hydrocarbons.*

By R. D. BROWN.

A new theoretical treatment of the diene synthesis is described. A quantity termed the para-localisation energy is defined, and the results of calculations of this quantity for various pairs of positions in some polycyclic aromatic hydrocarbons are reported. It is shown that these values can be used to predict correctly in every case whether a molecule is reactive, and the observed position of addition. The need for some experimental rate measurements is briefly indicated and the factors neglected and approximations involved in the proposed theory are enumerated.

THE mechanism of the Diels–Alder reaction has been the subject of a number of investigations. In particular it has been shown by stereochemical and kinetic evidence (Bergmann and Eschinazi, *J. Amer. Chem. Soc.*, 1943, **65**, 1405; Wassermann, *J.*, 1942, 612) that the activated complex has a configuration similar to that of the final addition product, *i.e.*, that the two new C–C bonds are formed simultaneously. Theoretical interpretations include Clar's (*Ber.*, 1931, **64**, 2194; 1932, **65**, 1521) involving biradical intermediates; an alternative explanation applicable vinyl derivatives of aromatic hydrocarbons has been proposed more recently (Daudel and Pullman, *J. Physique*, 1946, **7**, 105; *Compt. rend.*, 1945, **221**, 201; Daudel *et al.*, *Bull. Soc. chim.*, 1948, **15**, 1202), the dienic properties being associated with certain features of the molecular diagrams obtained by the method of mesomerism. However it is hard to see how either of these ideas could be applied semiquantitatively to determine relative reactivities of various molecules.

Evans and Warhurst (*Trans. Faraday Soc.*, 1938, **34**, 614) have given a detailed treatment of the kinetics of the dimerisation of butadiene, based on the theory of absolute reaction rates, and assuming the configuration of the activated complex mentioned above. Unfortunately more complex systems are not so susceptible to such a treatment.

The proposed theory combines the advantages of a semiquantitative treatment with applicability to a wider range of molecules. In many ways it is analogous to Wheland's treatment of aromatic substitution (*J. Amer. Chem. Soc.*, 1942, **64**, 900; Dewar, *J.*, 1949, 463). For the present we shall consider the addition of one particular dienophil (maleic anhydride) to various conjugated hydrocarbons; it is hoped later to extend the theory to cover the reactions of various dienophils with a particular hydrocarbon.

Assumptions of the Theory.—The formation of an adduct involves the localisation of two of the π-electrons of the conjugated hydrocarbons to form the two new σ C–C bonds. The fundamental assumption of the theory is that the ease of formation of an adduct at a pair of atoms, m and n, of the hydrocarbon depends only on the energy required to localise two of the π-electrons upon atoms m and n, *provided that* m *and* n *are orientated favourably*. This latter provision will be taken to be that m and n must lie para to one another in the case of a polycyclic hydrocarbon. It is proposed to term this energy quantity the *para-localisation energy* * of the pair of atoms m and n.

The above assumption is equivalent to assuming that the entropy of activation is constant for a given dienophil, and that the important variable part of the potential energy of activation is the para-localisation energy. If such assumptions are valid then it is also likely that the para-localisation energy is the important variable portion of the free energy of reaction; in other words it is likely that the products most rapidly formed will be the most stable. This " consequence " is important because in many cases it is not clear whether the experimentally isolated products are those most rapidly formed or those which are the most stable (from the equilibrium point of view); for the present theory we are justified in interpreting qualitative results in either of these two ways.

Computation of Para-localisation Energies.—The para-localisation energies may be computed by any of the standard approximate quantum-mechanical methods, but the molecular-orbital method, which has several advantages over other methods, particularly when large unsymmetrical molecules are concerned, has been used exclusively in the present work. Clearly from the definition of the para-localisation energy, P, we have:

$$P = E_r - E + 2\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where E is the π-electron energy of the original conjugated system, 2α the energy of two isolated π-electrons, and E_r is the total π-electron energy of the one or more separate conjugated systems left when the two π-electrons are localised upon atoms m and n. In keeping with previous terminology (Brown, *Aust. J. Sci. Res.*, *A*, 1949, **2**, 566) these conjugated systems will be termed collectively the residual molecule.

The energies E, E_r may be computed by assuming orthogonal atomic orbitals, or by including the overlap integral, whose value is generally assumed to be 0·25. The latter procedure is generally accepted as being more accurate, and it has been proposed (Brown, *Trans. Faraday Soc.*, in the press) to denote energy quantities computed by assuming an overlap integral of 0·25 by primed symbols, quantities computed by assuming orthogonal orbitals being represented by the corresponding unprimed symbols. In addition the former quantities are expressed in terms of the exchange integral, γ, the latter in terms of the exchange integral, β. Thus P', defined by

$$P' = E_r' - E' + 2\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

will be expressed in terms of γ, P, defined by equation (1), in terms of β. In general both P and P' will be listed for each pair of positions, but only P' will be converted into kcal. mol.$^{-1}$, the conversion factor, $\gamma = -34$ kcals., recommended by Dewar (*Trans. Faraday Soc.*, 1946, **42**, 767) being used for this purpose.

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* I am indebted to Professor C. A. Coulson for suggesting this name and the symbol P.

P and P' may alternatively be expressed in terms of resonance energies :

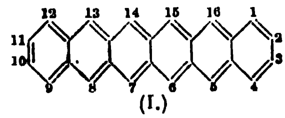
$$P = R - R_r - 2\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$P' = R' - R_r' - 1{\cdot}6\gamma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Before proceeding to the discussion of results obtained for various molecules we may notice a general principle which is apparent from inspection of equations (3) and (4), namely that for any given molecule the most reactive pair of positions will be those giving rise to the most stable residual molecule.

Results.—The results of calculations of P and P' are listed in Tables I—IV. Except where otherwise indicated in the Tables, the resonance energies involved have been calculated by direct solution of the relevant secular determinants. Differences in P' from the value $-2{\cdot}07\gamma$ for the 9 : 10 positions of anthracene have in many cases been converted into " theoretical " ratios of rate constants upon the assumption that $RT = 0{\cdot}6$ kcal. N represents the number of separate conjugated systems comprising the residual molecule. This will be referred to again later.

The para-localisation energies of the linear polyacenes (I) are shown in Table I. Two things are apparent. First the para-localisation energy of the most reactive pair of positions for a given molecule decreases with increasing size of the molecule, pointing to an increase in reactivity with increasing molecular weight. Secondly in any particular molecule the reactivity of successive pairs of " meso "-positions (pairs such as 1 : 4, 5 : 16, 6 : 15 in hexacene being classed as " meso " for convenience in discussion) increases as we move towards the centre of the molecule. From the results for an infinite strip it is clear that a limiting value of the reactivity is rapidly approached in both of these sequences.



(I.)

Many other possible pairs of positions have been excluded from consideration in the Tables by means of the principle that only pairs giving rise to sufficiently stable residual molecules will be reactive, and, on this qualitative principle, the positions listed are the most reactive of all possible pairs in each molecule.

TABLE I.

The Polyacenes.[a]

Molecule.	Positions.	$P(-\beta)$.	P', $(-\gamma)$.	P', kcals.	Relative rate.
Benzene	1 : 4	4·00	2·67	91	*ca.* 10^{-15}
Naphthalene	1 : 4	3·68	2·40	82	*ca.* 10^{-8}
Anthracene	1 : 4	3·63	2·34	80	*ca.* 10^{-7}
	9 : 10	3·31	2·07	70	1
Naphthacene	1 : 4	3·62	2·33	79	—
	5 : 12	3·25	2·01	68	30
Pentacene	1 : 4	3·61	2·33	79	—
	5 : 14	3·23	1·99	68	90
	6 : 13	3·18	1·94	66	1,600
Hexacene (I)	1 : 4	3·61	2·33	79	—
	5 : 16	3·23	1·99	68	90
	6 : 15	3·16	1·92	65	5,000
Infinite strip[b]	*a*	3·611	2·325	79	—
	b	3·223	1·984	67	—
	c	3·151	1·913	65	—
	d	3·132	1·893	64	—
	e	3·126	1·887	64	—
	f	3·124	1·885	64	—
	g	3·124	1·884	64	48,000

[a] N is 2 for all pairs of positions considered here. [b] Values for the limit of the polyacene series were computed by using asymptotic values for the resonance energies, R, R' (results in course of publication). The pairs of positions referred to by *a*, *b*, *c*, . . . are the successive " meso "-positions starting at one end of the strip; for example, on this system the pairs of positions in hexacene numbered 1 : 4, 5 : 16, 6 : 15 would be referred to as *a*, *b*, *c*, respectively.

The results given in Table I explain the experimental findings for the polyacenes. As benzene and naphthalene do not add maleic anhydride (Mameli, Pancotto, and Crestani, *Gazzetta*, 1937, **67**, 669; Alder, " Newer Methods of Preparative Organic Chemistry," 1948, p. 485; Clar, " Aromatische Kohlenwasserstoffe," 1941, p. 12) and anthracene on the other hand undergoes addition at the 9 : 10-positions (Clar, *Ber.*, 1931, **64**, 1682; *op. cit.*, p. 126; Diels and

Alder, *Annalen*, 1931, 486, 191) it appears that appreciable addition can be detected only when P is less than $-3{\cdot}6\beta$ or P' is less than $-2{\cdot}3\gamma$ (78 kcals./mole). In agreement with prediction naphthacene, pentacene, and hexacene add maleic anhydride at the central " meso "-positions with rapidly increasing ease (Clar, *Ber.*, 1932, 65, 503; 1931, 64, 2194; 1939, 72, 1817).

The critical values of P and P' just mentioned will be seen to predict correctly the course of the Diels–Alder reaction for all polynuclear hydrocarbons for which the experimental facts are known. Strictly, a given critical value of P' should apply only for a given experimental temperature (and possibly solvent) and for a given value of N. However, in the present paper almost all reactive positions correspond to $N = 2$. Also it might be necessary to specify different critical values for different dienophils. The experimental data are not sufficiently numerous to select any particular temperature as standard.

TABLE II.

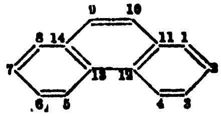
Molecule.	Positions.	N.	$P(-\beta)$.	P', $(-\gamma)$.	P', kcals.
Phenanthrene (II)	1 : 4	2	3·77	2·47	84
	9 : 12	2	4·46	2·88	98
	2 : 12	2	4·51	2·91	99
	4 : 5	1	4·37 [a]	—	—
Chrysene (III)	3 : 6	2	3·74	2·45	83
	8 : 16	2	4·33 [b]	—	—
	7 : 13	2	4·52	2·94	100
	6 : 7	1	4·57 [c]	—	—
3 : 4-Benzphenanthrene (IV)	1′ : 4′	2	3·74	2·45	83
	2 : 12	2	4·25	2·70	92
	1 : 4	2	4·52	2·93	100
	4′ : 13	1	5 [c]	—	—
Picene (V)	1 : 4	2	3·75	2·46	84
	6 : 16	2	4·51	2·92	99
	6 : 7	1	*ca.* 3·80 [c]	—	—
	1 : 14	1	*ca.* 3·97 [c]	—	—

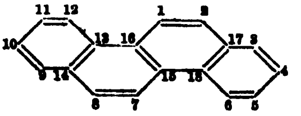
[a] The resonance energy of the residual molecule, R_r, was obtained from Syrkin and Diatkina's data (*Acta Physicochim.*, 1946, **21**, 641). [b] R_r was obtained from Berthier and Pullman's data (*Bull. Soc. chim.*, 1948, **15**, 554). [c] R_r was calculated from the redox potential of the corresponding quinone by an empirical method (in course of publication).

The para-localisation energies of some angular hydrocarbons are listed in Table II. All values listed are greater than those for 1 : 4-addition to naphthalene; this is in agreement with experimental observations (Jones, Gogek, and Sharpe, *Can. J. Research*, *B*, 1948, **26**, 719; Alder, *op. cit.*, p. 485; Clar, *Ber.*, 1932, **65**, 853; Clar and Lombardi, *ibid.*, p. 1413) that phenanthrene and chrysene will not react with maleic anhydride. The possibility of reaction of 3 : 4-benzphenanthrene or picene with maleic anhydride does not seem to have been investigated. The present results indicate that no addition will take place with these hydrocarbons; a result to be expected from the principle that " only molecules containing the anthracene skeleton will react." It will also be noticed that the reactivity, as indicated by the smallest value of the para-localisation energy for each molecule, remains almost constant.

Values of P and P' for some molecules related to anthracene are presented in Table III (it will be noticed that N is 2 for all pairs of positions considered). These indicate that addition will occur in each case, the " meso "-positions of the anthracene portions being attacked preferentially, and the ease of addition decreasing in the sequence: 1 : 2-benznaphthacene, anthracene, 4 : 5-benzchrysene, 1 : 2-benzanthracene, pentaphene, 1 : 2-3 : 4-dibenzanthracene, 1 : 2-7 : 8-dibenzanthracene, 1 : 2-5 : 6-dibenzanthracene, the last two being of almost identical reactivity (calculations to a greater number of significant figures for P' predict relative reaction rates of 1 : 1·07 for these two compounds) so that the actual relative reactivities will probably be more dependent upon factors which are ignored in the present treatment for simplicity (*e.g.*, entropy of activation). This sequence agrees with all available experimental facts. 1 : 2-Benzanthracene is more difficultly reactive than anthracene (Clar, *Ber.*, 1932, **65**, 519; "Aromatische Kohlenwasserstoffe," p. 133), in sharp contrast to its isomer, naphthacene (see above). This is

(II.)





(III.)

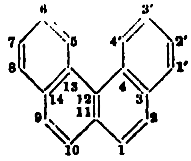
TABLE III.

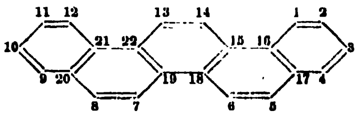
Molecule.	Positions.	$P(-\beta)$.	P', $(-\gamma)$.	P', kcals.	Relative rate.
Anthracene	1 : 4	3·63	2·34	79	—
	9 : 10	3·31	2·07	70	1
1 : 2-Benzanthracene[a]	1′ : 4′	3·78	2·49	85	—
	5 : 10	3·41	2·17	74	0·003
	6 : 9	3·64	2·36	80	—
1 : 2-3 : 4-Dibenzanthracene	1′ : 4′	3·83	2·55	87	—
	5 : 10	3·49	2·24	76	0·00006
	6 : 9	3·70	—	—	—
1 : 2-5 : 6-Dibenzanthracene	1′ : 4′	3·79	2·49	85	—
	5 : 10	3·51	2·26	77	0·00002
1 : 2-7 : 8-Dibenzanthracene	1′ : 4′	3·79	2·49	85	—
	5 : 10	3·51	2·26	77	0·00002
Pentaphene (2 : 3-6 : 7-dibenzphenanthrene)	1 : 4	3·67	2·38	81	—
	5 : 14	3·45	2·20	75	0·0006
1 : 2-Benznaphthacene[a]	1′ : 4′	3·80	2·49	85	—
	5 : 12	3·36	2·11	72	0·1
	6 : 11	3·28	2·03	69	10
	7 : 10	3·64	2·34	79	—
4 : 5-Benzchrysene[b]	9 : 12	3·74	2·45	83	—
	3 : 6	3·38	2·14	73	0·02
	1′ : 4′	3·64	2·36	80	—

[a] The resonance energies of these compounds were computed by using an empirical method based upon the concept of " annelation energy " (in course of publication).

an excellent example of the different effects of linear and angular annelation upon the resonance energy of a polycyclic hydrocarbon (the residual molecule is the same for " meso "-addition to these two hydrocarbons), and can be shown to be related to the difference in mobile order of the 1 : 2- and the 2 : 3-bond in anthracene (results in course of publication). 1 : 2-5 : 6-Dibenzanthracene reacts considerably less readily than anthracene with maleic anhydride (Cook, *J.*, 1931, 3273), and pentaphene adds two molecules of maleic anhydride at a much slower rate than anthracene, at the positions predicted in Table 3 (Clar, *Ber.*, 1931, **64**, 2195). It will be observed that addition of one molecule of maleic anhydride to the 5 : 14-positions of pentaphene results in a molecule of adduct which in the present treatment must be regarded as anthracene; thus the second addition occurs at the " meso "-positions in the anthracene system, which corresponds to the 8 : 13-positions in the pentaphene system, and so must be expected to take place more rapidly than the addition of the first molecule of dienophil. The experimental data for 1 : 2-benznaphthacene, 4 : 5-benzchrysene, and 1 : 2-3 : 4-dibenzanthracene are also in excellent accord with the theory. Clar and Lombardi (*ibid.*, 1932, **65**, 1419) noted qualitatively that the order of reactivity is that predicted by the present theory. The relative rates deduced from differences in P' will be noticed to be 1,000,000 : 2,000 : 1 but these are expected to be too great because complete localisation is assumed in the activated complex. This makes the calculated values of P' too great and the effect is not wholly cancelled when differences in P' are considered. Hence when these are converted into kcals. with the conversion factor which is known (Dewar,

(IV.)





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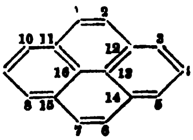

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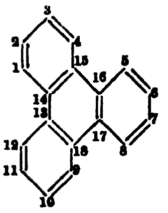

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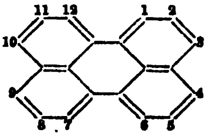

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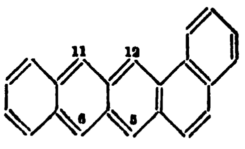

(IX.)

Trans. Faraday Soc., 1946, **42**, 767) to give excellent values for resonance energies, the resultant differences in activation energy will necessarily be too great. The predicted relative rates are of course exponential functions of the activation-energy differences and so are very sensitive to the absolute magnitudes of the latter. This could be overcome by choosing a value for γ which gives satisfactory relative rates, but in view of the approximations inherent in the present treatment it is unlikely that anything more reliable than the order of magnitude of relative rates could be estimated by this method. In this connection comparative measurements of the rates of addition for some of the hydrocarbons listed in Table III would be valuable, and the case of 1 : 2-7 : 8- and 1 : 2-5 : 6-dibenzanthracene is particularly interesting in view of the very slight difference (0·0012γ) in P' for these two compounds (see above).

The theoretical results for 1 : 2-benznaphthacene, in addition to predicting the correct reactivity relative to the other related molecules, also lead to the correct conclusion about the position of addition. Thus of the two possible pairs of positions, shown in (IX), which are expected to be reactive on empirical grounds, it is 6 : 11 which undergoes addition, as the present theory predicts. This could not have been predicted by the existing empirical principles.

TABLE IV.

				P',	
Molecule.	Position.	N.	$P(-\beta)$.	$(-\gamma)$.	kcals.
Diphenyl	1 : 4	3	4·38	2·78	95
	2 : 5	2	3·96	2·64	90
	2 : 2′	1	4·33	3·01	102
p-Terphenyl [a]	1 : 4	3	4·39	2·79	95
	2 : 5	2	3·96	2·64 [b]	90
	2′ : 5′	2	3·92	2·62	89
p-Quaterphenyl [a]	1 : 4	3	4·39	2·79	95
	2 : 5	2	3·96 [c]	2·64 [c]	90
	2′ : 5′	2	3·92	2·61	89
Pyrene (VI)	3 : 14	2	4·38 [d]	2·79 [d]	95
	6 : 16	1	4·50 [d]	2·93 [d]	100
	11 : 12	2	5·43 [e]	—	—
Triphenylene [e] (VII)	1 : 4	2	3·79	—	—
	2 : 15	2	4·42	—	—
	13 : 16	2	5·19	—	—
	1 : 12	1	4	—	—
Perylene (VIII)	1 : 12	1	3·92 [d]	2·60 [d]	88

[a] The resonance energies of these molecules were computed from the empirical equations for the conjugation energies (Brown, *Aust. J. Sci. Res.*, *A*, 1949, **2**, 566; other results in course of publication). [b] R' for the residual molecule was calculated from the empirical equation for the conjugation energy, C'. [c] The conjugation energies, C and C', were estimated for calculation of R and R'. [d] The resonance energies of the residual molecules, R_r, R_r', were calculated from C and C'. [e] The value used for the resonance energy of this molecule was that given by Syrkin and Diatkina (*loc. cit.*).

The para-localisation energy of some miscellaneous hydrocarbons are presented in Table IV. From the critical values for P and P' suggested above it would be expected that none of the molecules listed would add maleic anhydride. The experimental observations agree with this prediction in the case of diphenyl and pyrene (Arbuzov, Salmina, and Sharpshinskaya, *Trans. Butlerov Inst. Chem. Tech. Kazan*, 1934, No. 2, 9; Clar, *Ber.*, 1936, **69**, 1683) but at first sight the reaction reported for perylene (Clar, *ibid.*, 1932, **65**, 846) appears to form an exception to the present theory. However it is significant that the product isolated is not the adduct but the corresponding dehydrogenated compound. It seems likely that the factor which produces this product is an irreversible disturbance of the equilibrium between the adduct and its components (and very much in favour of the components as judged by the value of P') by oxidation by the solvent, nitrobenzene. Further weight is lent to this interpretation by Clar's observation that no detectable reaction occurs in boiling xylene, and also that prolonged heating at the relatively high temperature of boiling nitrobenzene was required to obtain a satisfactory reaction.

It may be remarked in passing that the lack of reactivity noted for some of the other molecules considered above may be due to the setting up of an unfavourable equilibrium just as much as due to a very small rate constant because if the value of P or P' is a satisfactory criterion these two phenomena will run parallel (see above).

The above study of some 24 hydrocarbons shows that the proposed theory of the Diels–Alder reaction is completely satisfactory to the present extent of experimental knowledge. The empirical fact that molecules containing the anthracene skeleton are in general reactive and the more angular molecules unreactive is convincingly explained by the fact that the former can give rise to relatively stable residual molecules whereas the latter cannot. In addition the relative reactivities of reactive hydrocarbons can readily be interpreted; indeed it is possible to interpret these relative reactivities in a general qualitative way, as will be described in a later paper of this series.

Approximations and Neglected Factors.—As mentioned above, variations in the entropy of activation are neglected in the present theory, variations in reaction rate being assumed to be due only to variations in the potential energy of activation. Formation of the activated complex will presumably involve partial localisation of two of the π-electrons of the hydrocarbon, together with two of its carbon atoms, m and n, which are now linked to the dienophilic portion by incipient σ-bonds. The energy of activation will include the energy of formation of the latter bonds together with energy changes accompanying any change in the spatial configuration of the hydrocarbon portion. The assumption has been made that any such contributions are approximately constant from molecule to molecule, and attention has then been focussed upon variation in the π-electron energy changes.

As the atoms m and n are not completely localised in the transition state the residual molecule will be more stable than has been assumed above by an amount equal to the conjugation energy of the various separate conjugated systems through atoms m and n. Qualitatively we might expect this conjugation energy to increase with increase in N, the number of separate systems comprising the residual molecule. Consequently if two pairs of positions have the same para-localisation energy we should expect the one with the greater N to be the more reactive.

Another approximation involved in the present theory is the calculation of the para-localisation energy by an approximate method. However the systems involved are always neutral molecules and Dewar (*Trans. Faraday Soc.*, 1946, **42**, 767) has shown that the molecular-orbital method gives very satisfactory resonance energies in such cases. It will be observed that the proposed theory applies equally well to the "ionic" mechanism favoured by Woodward (*J. Amer. Chem. Soc.*, 1942, **64**, 3058) for the diene synthesis. In the latter case we have merely to replace the assumption that a system of two isolated carbon atoms, each carrying one π-electron, has an energy approximately constant from molecule to molecule, by the analogous assumption that a system of two isolated carbon atoms, one carrying two π-electrons, the other none, has the same property. For convenience the energy of either system may be assumed to be 2α to simplify the values of P and P'.

The para-localisation-energy concept has been applied to some other polycyclic hydrocarbons for which the experimental investigation has not been made. These results and others for vinyl and phenyl derivatives of aromatic hydrocarbons will be presented in Part II.

UNIVERSITY OF MELBOURNE, VICTORIA, AUSTRALIA.

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139. *The* Euphorbia *Resins. Part III. The Epimerisation and Dehydration of Euphol.*

By RALPH N. E. BENNETT and FRANK L. WARREN.

Euphone is reduced with difficulty by aluminium *iso*propoxide to give epi*euphol* (hydrogenated to *dihydro*epi*euphol*), which is not identical with any of the known tetracyclic triterpene alcohols. Similar reduction of dihydroeuphone gave dihydroeuphol. *Euphyl toluene*-p-*sulphonate* in boiling acetic acid or pyridine gave *euphatriene* which was hydrogenated to euphene.

IN view of the isolation from the *Euphorbia* species of several isomeric tetracyclic triterpene alcohols, $C_{30}H_{50}O$, containing an *iso*propylidene group and an inactive double bond, it became of interest to prepare the hydrocarbon, ketone, and epimeric form of the principal constituent euphol for comparison purposes. Whilst this work was in progress, Roth and Jeger (*Helv. Chim. Acta*, 1949, **32**, 1625) reported the dehydrogenation of euphol and dihydroeuphol to euphone and dihydroeuphone, respectively, which have properties in agreement with our findings. We have observed, however, that these dehydrogenations are effected in higher yields with copper oxide (cf. Diels and Abderhalden, *Ber.*, 1904, **37**, 3099) than with precipitated copper. Euphone is not an αβ-unsaturated ketone since the light-extinction curve which shows $\lambda_{max.}$ 210 mμ. (log $\varepsilon_{max.}$ 3·7) and $\lambda_{max.}$ 295 mμ. (log $\varepsilon_{max.}$ 1·4) is identical in the ultra-violet with that of euphyl acetate. Dutta and Karimulla (*J. Sci. Ind. Res. India*, 1944, **3**, 212) report that the dried latex from *E. tirucalli* yielded a ketone, $C_{27}H_{42}O$. We have failed to isolate a ketone from the fresh latex (cf. Haines and Warren, *J.*, 1949, 2554), and this ketone is probably formed during the drying, for the *Euphorbia* latices readily give positive tests for indirect oxidases. This ketone is certainly identical with euphone (see table below), the formula for which follows from the rigid establishment of euphol as $C_{30}H_{50}O$ by McDonald, Warren, and Williams (*J.*, 1949, S 155).

	This paper.		Dutta and Karimulla.	
		M. p.		M. p.
Euphone	$C_{30}H_{50}O$	117—118°	$C_{27}H_{42}O$	119°
Euphoxime	$C_{30}H_{49}ON$	192—193	Oxime	194—195
Dihydroeuphoxime ...	$C_{30}H_{51}ON$	205—206	Tetrahydro(?)-oxime	207—208

Catalytic reduction of euphone in the presence of Adams's catalyst at atmospheric pressure gave dihydroeuphone as reported by Roth and Jeger (*loc. cit.*), but under pressure dihydroeuphol was obtained. Attempts to reduce euphone by the Meerwein–Pondorff–Verley reaction, using the standard procedure of refluxing with *iso*propyl alcohol as solvent, gave, even after prolonged treatment, pure euphone in quantitative yield. By carrying out the reaction in toluene (cf. Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 461) or in *iso*butanol (cf. Malcom and Read, *J.*, 1939, 1037) it was possible to obtain small quantities of *epi*euphol, $C_{30}H_{50}O$, m. p. 125°, $[\alpha]_D^{20}$ +22·6°, yielding an *acetate*, m. p. 112—113°, $[\alpha]_D^{20}$ −66°. The small quantity of *epi*euphol was readily eluted from a column of alumina and the residual product, which was more strongly adsorbed, gave no pure substance. The difficulty of reducing euphone by the Meerwein–Pondorff–Verley reaction may be attributed to the keto-group's being sterically hindered, and is interesting in the light of the statement made by Newbold and Spring (*J.*, 1944, 250) that "the ease with which euphol is washed from alumina with light petroleum is remarkable and .... this property is probably of constitutional significance."

Catalytic reduction of *epi*euphyl acetate at atmospheric pressure in the presence of Adams's catalyst gave an acetate, m. p. 108—110°, which showed no depression when mixed with starting material (it was at first thought that the dihydro-compound had not been formed). Reduction of *epi*euphol under pressure gave *dihydro*epi*euphol*, $C_{30}H_{52}O$, m. p. 128—129°, $[\alpha]_D^{20}$ +33·9°, which showed a decided depression when mixed with *epi*euphol. It yielded an *acetate*, $C_{32}H_{54}O_2$, m. p. 111°, $[\alpha]_D^{20}$ −61·2°, which, when mixed with *epi*euphyl acetate, m. p. 112—113°, was depressed only to 108—110°. Attempts to obtain dihydro*epi*euphol by the reduction of dihydroeuphone with aluminium *iso*propoxide or with sodium and *iso*propyl alcohol gave only dihydroeuphol as the isolable product.

It is of interest that attempts to epimerise euphol by boiling *euphyl toluene*-p-*sulphonate* with acetic acid (cf. Plattner and Fürst, *Helv. Chim. Acta*, 1943, **26**, 2266) gave *euphatriene*, which was also obtained by boiling the toluenesulphonate with pyridine. This euphatriene was hydrogenated catalytically to euphene having physical properties identical with those reported by Roth and Jeger (*loc. cit.*) for euphene obtained by Wolff–Kishner reduction of euphone.

EXPERIMENTAL.

(Microanalyses were by Drs. Weiler and Strauss, Oxford. All m. p.s are uncorrected.)

Euphone.—(*a*) Euphol (2 g.) and dry, freshly precipitated copper (4 g.) were heated at 330—340° for 12 minutes, and the product distilled at 180—240°/5 mm. to give a glassy solid. Crystallisation from methanol–acetone and finally from ethanol gave euphone as stout needles, m. p. 117—118°, $[\alpha]_D^{20}$ +78·2° (*c*, 1 in chloroform) (Found: C, 84·65; H, 11·0. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%). Roth and Jeger (*loc. cit.*) give m. p. 119—120°, $[\alpha]_D^{20}$ +69°. *Euphone oxime* crystallised from ethanol in colourless plates, m. p. 192—193°, $[\alpha]_D^{20}$ +7·5° (*c*, 1 in chloroform) (Found: C, 82·0; H, 11·0. $C_{30}H_{49}ON$ requires C, 81·9; H, 11·2%).

(*b*) Euphol (2 g.) was heated to 300° for 15 minutes in an atmosphere of carbon dioxide, and copper oxide (0·4 g.) added slowly. The product in light petroleum (b. p. 50—70°) was chromatographed through alumina (25 g.). Light petroleum (250 ml.) eluted a solid which was crystallised as above to give 1·6 g. of pure euphone. This method was preferred to method (*a*).

Dihydroeuphone.—(*a*) Dihydroeuphol, oxidised with copper oxide as above and crystallised from ethanol, gave dihydroeuphone, m. p. 64°. Roth and Jeger (*loc. cit.*) give m. p. 68°. *Dihydroeuphone oxime* crystallised from ethanol in colourless pearly plates, m. p. 205—206°, $[\alpha]_D^{20}$ +3° (*c*, 1 in chloroform) (Found: C, 82·2; H, 11·65; N, 3·2. $C_{30}H_{51}ON$ requires C, 81·7; H, 11·6; N, 3·2%). (*b*) Catalytic hydrogenation of euphone gave dihydroeuphone identical with the above.

Dihydroeuphol.—(*a*) Euphone (1 g.), hydrogenated with Adams's catalyst at 50 atm. pressure, gave quantitatively dihydroeuphol, m. p. 117—118°, undepressed with authentic specimen. (*b*) Dihydroeuphone (1 g.) was treated with aluminium *iso*propoxide in toluene as described below for the preparation of *epi*euphol. Chromatographic analysis of the product in ether and two crystallisations from methanol gave only dihydroeuphol, as felted needles, m. p. 120—121°, undepressed on admixture with an authentic specimen. (*c*) Dihydroeuphone (250 mg.) and *iso*propyl alcohol (38 ml.) were refluxed with sodium (1·25 g.)

for 1 hour. The solution was poured into water and extracted with ether, and the ethereal extract washed with water and dried. The ethereal solution gave a gum which was treated with acetic anhydride (3 ml.) and pyridine (1·8 ml.) and worked up in the usual way. The product, twice crystallised from methanol, gave dihydroeuphyl acetate, m. p. 122—124°, undepressed on admixture with an authentic specimen.

epi*Euphol.*—(*a*) Euphone (1 g.), freshly distilled aluminium *iso*propoxide (2 g.), and *iso*butyl alcohol (20 ml.) were refluxed in an oil-bath at 160°. After each hour *iso*butyl alcohol (10 ml.) was added, and 10 ml. were allowed to distil off. After 6 such operations a further quantity of aluminium *iso*propoxide (4 g.) was added to replace loss and hasten the reaction. The product was steam-distilled and then acidified with dilute sulphuric acid, and the dried ethereal extract was chromatographed through alumina (20 × 2 cm.). The first 180 ml. eluted a solid (200 mg.), m. p. 117—119°, which, crystallised twice from acetone and twice from methanol, gave epi*euphol* as fine felted needles, m. p. 125°, $[\alpha]_D^{20}$ +22·6° (*c*, 0·9 in chloroform) (Found: C, 84·4; H, 12·0. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Mixed m. p.s with euphol, m. p. 116°, and dihydroeuphol, m. p. 120—121·5°, gave depressions to 88—94° and 90—95°, respectively. Further elution of the column gave a solid, m. p. *ca.* 50—70°, from which a pure component could not be isolated.

(*b*) Euphone (1 g.) and aluminium *iso*propoxide (15 g.) in dry toluene (20 ml.) were refluxed in an oil-bath for 4 hours. Absolute *iso*propyl alcohol was added and then distilled off. The ethereal extract gave a solid which was dissolved in ether and chromatographed through alumina (22 × 2 cm.). The first 100 ml. of ether eluted a solid (200 mg.), m. p. 117—120°, which gave as above *epi*euphol. Light petroleum proved less satisfactory for the chromatogram.

epi*Euphyl Acetate.*—*epi*Euphol (300 mg.), acetic anhydride (9 ml.), and pyridine (2 ml.) were heated at 100° for 4 hours. The solid product was dissolved in chloroform, and the solvent gradually replaced by methanol, from which epi*euphyl acetate* crystallised on cooling in highly refractive plates, m. p. 112—113°, $[\alpha]_D^{20}$ −66° (*c*, 0·95 in chloroform), unchanged by further crystallisation (Found: C, 82·0; H, 11·2. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

*Dihydro*epi*euphol.*—(*a*) *epi*Euphyl acetate (250 mg.) in ethyl acetate (12 ml.) and glacial acetic acid (3 ml.) was reduced in the presence of platinic oxide (30 mg.). Absorption of hydrogen (11·9 ml. at N.T.P. Calc. for $C_{32}H_{52}O_2$: 1 mol. = 11·2 ml.) was complete after 10 hours. The product crystallised from methanol in plates, m. p. 108—110°, showing no depression when mixed with *epi*euphyl acetate.

(*b*) *epi*Euphol (250 mg.) in ethanol (100 ml.) was hydrogenated in the presence of platinic oxide (300 mg.) at 80 atm. pressure for 6 hours. The product crystallised from methanol to give *dihydro*epi*euphol* as felted needles, m. p. 128—129°, $[\alpha]_D^{20}$ +33·9° (*c*, 0·73 in chloroform) (Found: C, 84·1; H, 12·0. $C_{30}H_{52}O$ requires C, 84·05; H, 12·2%). A mixture with *epi*euphol had m. p. 108—110°. Acetylation in the presence of pyridine and crystallisation of the product from methanol gave *dihydro*epi*euphyl acetate* as highly refractive plates, m. p. 111°, $[\alpha]_D^{20}$ −61·2° (*c*, 0·97 in chloroform) (Found: C, 81·8; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·55%). The m. p. of a mixture with *epi*euphyl acetate, m. p. 112—113°, was 108—110°.

Oxidation of epi*Euphol.*—epi*Euphol* (250 mg.) was heated with copper oxide (50 mg.) at 300° for 10 minutes in an atmosphere of carbon dioxide. The product was chromatographed through alumina (10 g.) with light petroleum to yield a solid which crystallised from ethanol as needles, m. p. 115—116°, showing no depression when mixed with euphone.

*Euphyl Toluene-*p*-sulphonate.*—Euphol (5 g., 1 mol.), pyridine (50 ml.), and toluene-*p*-sulphonyl chloride (5 g., 2 mols.) were allowed to react at 20° for 18 hours, and then poured into water. The ethereal extract, washed with dilute hydrochloric acid and dried, was chromatographed through alumina (30 g.). Crystallisation from acetone–water and twice from methanol gave *euphyl toluene-*p*-sulphonate* as felted needles, m. p. 103·5—104·5° (Found: C, 76·3; H, 9·7. $C_{37}H_{56}O_3S$ requires C, 76·5; H, 9·65%).

Euphatriene.—Euphyl toluene-*p*-sulphonate (5 g.), dry powdered calcium carbonate (6 g.), and pyridine (50 ml.) were refluxed for 2 hours under anhydrous conditions. The product was poured into water, and the ethereal extract, washed with acid, gave an oil. One chromatographic separation through alumina gave a solid which still contained a trace of sulphur. The product was hydrolysed with alcoholic potash and rechromatographed with ether as solvent. The oily solid was crystallised four times from acetone to give *euphatriene* as stout, long, colourless needles, m. p. 116—117°, $[\alpha]_D^{20}$ +115·8° (*c*, 1 in chloroform) (Found: C, 88·2; H, 11·8; Found, after sublimation: C, 88·3; H, 11·7. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%).

Euphene.—Euphatriene (300 mg.) in ethyl acetate–acetic acid (1 : 1; 250 ml.) was hydrogenated in the presence of Adams's catalyst. The product crystallised from acetone to give euphene as needles, m. p. 58—60°, $[\alpha]_D^{20}$ +37·6° (*c*, 1·03 in chloroform) (Found: C, 87·6; H, 12·4. Calc. for $C_{30}H_{52}$: C, 87·3; H, 12·7%), unchanged by hydrogenation under pressure. Roth and Jeger (*loc. cit.*) give m. p. 60·5—61°, $[\alpha]_D^{20}$ +34°.

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Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa.

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oily acid which could not be induced to crystallise, and which gave a bis-*p*-phenylphenacyl ester, m. p. 98°, undepressed when mixed with the corresponding ester of dihydrosenecic acid.

Ozonolysis.—*trans*-Senecic acid (250 mg.) was dissolved in dry ethyl acetate and a stream of dry ozone passed through at 0° for ½ hour. The viscous, yellow, pungent ozonide was treated with water and warmed in a stream of carbon dioxide. The issuing acetaldehyde was passed into water and treated with dimedon; a flocculent precipitate was obtained which, when heated under reflux with one drop of hydrochloric acid in 80% ethanol (4 ml.) and cooled, gave flat crystals, m. p. 175—176°, undepressed on mixing with the octahydroxanthen derivative of acetaldehyde.

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Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa.
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141. *The* Senecio *Alkaloids. Part VII. The Structure of Retrorsine and Isatidine: The Ester Groupings.*

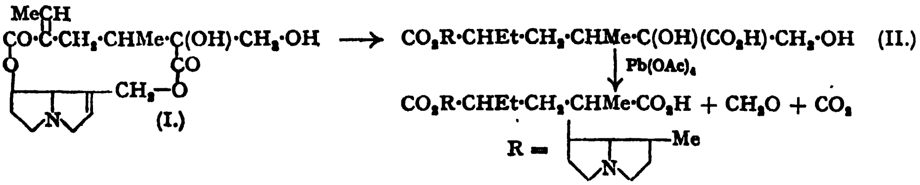
By Ernest C. Leisegang and Frank L. Warren.

Isatidine is reduced to retronecanyl dihydroisatinecate (dihydroretronecate) (II) which with lead tetra-acetate in aqueous acetic acid gives one mole of carbon dioxide. Thus in isatidine (retrorsine *N*-oxide) and retrorsine (I), the 2-carboxylic group of *cis*-1 : 2-dihydroxy-3-methylhept-5-ene-2 : 5-dicarboxylic acid (isatinecic acid) is esterified by the hydroxymethyl group of isatinecine and retronecine, respectively. The structure of similar *Senecio* alkaloids is indicated.

Isatidine is the ester of isatinecine, which Leisegang and Warren (*J.*, 1949, 486) showed to be retronecine *N*-oxide, with isatinecic acid, which Christie, Kropman, Novellie, and Warren (*J.*, 1949, 1703) gave as *cis*-1 : 2-dihydroxy-3-methylhept-5-ene-2 : 5-dicarboxylic acid. The general structure of isatidine is in conformity with de Waal's observation (*Onderstepoort J. Vet. Sci. Animal Husb.*, 1940, **14**, 445) that catalytic reduction gave octahydroanhydroisatidine, formulated as the dihydroisoatinecic (dihydroretronecic) ester of retronecanol by Christie, Kropman, Leisegang, and Warren (*J.*, 1949, 1700). We have now confirmed the structure of this reduction product by its hydrolysis to retronecanol, characterised as its picrate, and dihydroisatinecic acid, identified as its *p*-phenylphenacyl ester. Hydrogenolysis occurs at the carboxyl group esterified by the hydroxymethyl grouping of isatinecine.

To determine the orientation of the acid in isatidine we treated the reduced isatidine with lead tetra-acetate in acetic acid containing a small quantity of water. Carbon dioxide was immediately evolved as would be expected if the 2-carboxylic grouping were not esterified. The evolution of gas did not take place in anhydrous solvents; but the addition of a little water started the reaction so that the lead tetra-acetate caused fission of the glycol grouping to leave a keto-acid which was attacked by the reagent only in the presence of hydroxyl-forming compounds (cf. Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 1597). Since the quantity of carbon dioxide which dissolves in glacial acetic acid is large and varies considerably with the partial pressure of the gas (cf. Just, *Z. physikal. Chem.*, 1901, **37**, 342), the acetic acid was saturated and the reaction vessel filled with carbon dioxide before mixing the reagents. Only when the importance of this was pointed out by Dr. H. A. E. Mackenzie of these laboratories were we able to obtain quantitative yields of carbon dioxide. No evolution of gas was observed on treating either isatidine or retrosine with lead tetra-acetate under similar conditions.

The reduction of isatidine gave an oily product and hydrolysis of the alkaloid might have occurred during hydrogenation. Continuous ether extraction of the reduction product in hydrochloric acid gave, however, a negligible residue. On the other hand, previous hydrolysis of the reduced isatidine with barium hydroxide followed by continuous ether extraction of the acidified product for the same time gave an 80% yield of dihydroisatinecic acid:



(I.)

$$CO_2R{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}OH \quad \text{(II.)}$$

$$\downarrow Pb(OAc)_4$$

$$CO_2R{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H + CH_2O + CO_2$$

These results lead to the structure of retronecanyl dihydroisatinecate (dihydroretronecate) (II) and hence to retrorsine (I) and isatidine, which Christie, Kropman, Leisegang, and Warren (*loc. cit.*) showed to be retrorsine *N*-oxide.

The "necine" bases so far investigated may be formulated as derivatives of retronecine, *e.g.* platynecine (dihydroretronecine) (Adams and Rogers, *J. Amer. Chem. Soc.*, 1941, **63**, 228) and rosmarinecine (hydroxydihydroretronecine) (Richardson and Warren, *J.*, 1942, 452). In view of the structural similarity of senecic and integerrinecic (*trans*-senecic) acids with isatinecic (hydroxysenecic) and retronecic (*trans*-hydroxysenecic) acids, respectively (Christie, Kropman, Novellie, and Warren, *loc. cit.*; Kropman and Warren, *J.*, 1949, 2852), the orientation of these acids in the complete alkaloids (shown below as derivatives of retronecine and senecic acid) is probably similar.

Senecionine[a] = retronecine + senecic acid.
Integerrimine[b] = retronecine + *trans*-senecic acid.
Platyphylline[c,d] = dihydroretronecine + senecic acid.
Rosmarinine[d] = hydroxydihydroretronecine + senecic acid.

[a] Barger and Blackie, *J.*, 1936, 743; [b] Manske, *Canad. J. Res.*, 1939, **17**, 1; [c] Orekhov and Tiedebel, *Ber.*, 1935, **68**, 650; with Konovalova, *ibid.*, 1186; [d] de Waal and Tiedt, *Onderstepoort J. Vet. Sci. Animal Husb.*, 1940, **15**, 251; Richardson and Warren (*loc. cit.*).

EXPERIMENTAL.

Retronecanyl Dihydroisatinecate (*Dihydroretronecate*).—Isatidine (4·70 g., 1 mol.) in 0·47N-sulphuric acid (50 ml., 4 mols.) and Adams's catalyst (130 mg.) were shaken with hydrogen at room temperature and 20 atmospheres pressure for 6 hours. The filtered solution was treated with just sufficient 0·4N-barium hydroxide to precipitate the sulphuric acid, and the filtered solution was evaporated under reduced pressure giving retronecanyl dihydroisatinecate as a clear oil which did not crystallise when kept. This product (1·01 g., 1 mol.) was boiled with barium hydroxide octahydrate (1·07 g., 1·2 mols.) in water (20 ml.) for ½ hour, cooled, acidified with hydrochloric acid, and extracted with ether for 6 hours. The ethereal extract gave dihydroisatinecic acid (530 mg., 0·8 mol.), which was characterised as its *p*-phenylphenacyl ester, m. p. 124—127°, undepressed when mixed with an authentic specimen (Christie *et al.*, *J.*, 1949, 1700). The aqueous solution gave retronecanyl picrate, m. p. 205—207° (Barger *et al.*, *J.*, 1935, 11, give m. p. 208°).

Retronecanyl dihydroisatinecate was acidified with hydrochloric acid and extracted under similar conditions. The ether extract gave a negligible residue.

Action of Lead Tetra-acetate on Retronecanyl Dihydroisatinecate.—Glacial acetic acid (10 ml.) was placed in a flask connected to a gas burette containing brine, and dry carbon dioxide swept through to saturate the acetic acid and to displace all the air. An excess of lead tetra-acetate was added and then retronecanyl dihydroisatinecate (280 mg., 1 mol.). No reaction was observed. Without opening the apparatus a small quantity of water was squirted into the mixture whereupon carbon dioxide was evolved (observed: 18·3 ml. at N.T.P. Calc. for $C_{18}H_{31}O_6N$: 18·7 ml.). Isatidine under similar conditions gave no carbon dioxide during 12 hours.

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DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY,
UNIVERSITY OF NATAL, PIETERMARITZBURG, S. AFRICA. [*Received, November 7th, 1949.*]

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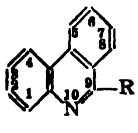
142. *Some Heterocyclic* N-*Oxides.*

By P. MAMALIS and V. PETROW.

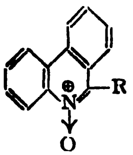
Although the preparation of some *phenanthridine* N-*oxides* has been accomplished, attempts to obtain the "*N*-oxide" analogue of Dimidium bromide (II) have proved unsuccessful.

By the action of phosphorus oxychloride on 9-*phenylphenanthridine* N-*oxide*, 3-*chloro*-9-*phenylphenanthridine* has been obtained. 9-*Methylphenanthridine* N-*oxide* similarly gave 9-chloromethylphenanthridine together with what was probably a 3-*chloro*-9-*methylphenanthridine*.

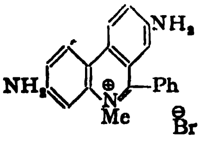
IN 1941 McIlwain (*Nature*, **148**, 628) reported that iodinin, the pigment of *Chromobacterium iodinum*, showed marked antibacterial action on a number of organisms. Chemical work on its structure revealed that the compound was a dihydroxyphenazine di-*N*-oxide, a result which led McIlwain (*J.*, 1943, 322) to the synthesis of a number of phenazine and quinoxaline di-*N*-oxides which showed varying degrees of antibacterial action. In 1943 White and Hill (*J. Bact.*, 1943, **45**, 433) reported the isolation of the antibiotic "aspergillic acid" which possessed an antibacterial range greater than that of penicillin (see Glister, *Nature*, 1941, **148**, 470) and proved to be a hydroxypyrazine *N*-oxide (see Newbold and Spring, *J.*, 1947, 372). The existence of *N*-oxide residues in at least two naturally occuring antibacterial agents appeared significant, particularly as the corresponding " deoxido "-compounds were without biological interest. We therefore undertook the preparation of some phenanthridine *N*-oxides (I*a*) for study as antibacterial agents and, as *N*-oxides bear an electronic resemblance to quaternary salt (*e.g.*, II), for examination as trypanocides. In particular, we wished to prepare the " *N*-oxide " analogue of the effective trypanocide, Dimidium bromide (II) (see Walls, *J.*, 1945, 294). Some new *quinoline* and *quinoxaline* N-*oxides* were also prepared, as we required a range of compounds which could function as mild oxidising agents for chemotherapeutic studies employing the anaerobic organism *Entamoeba histolytica.*



(I.)



(I*a*.)



(II.)

Conversion of phenanthridine itself, and of its 9-methyl and 9-ethyl derivatives, into the corresponding N-*oxides* was smoothly achieved by employing perphthalic acid. Peracetic acid, however, proved to be the reagent of choice for the preparation of the 9-arylphenanthridine *N*-oxides, which generally differed from their 9-alkyl analogues in failing to liberate iodine from potassium iodide under the experimental conditions specified by McIlwain (*J.*, 1943, 342) for this test.

The mononitrophenylphenanthridines were converted into their N-*oxides* with somewhat greater difficulty and required longer reaction periods with peracetic acid. This result is probably due to the electron-attracting effect of the nitro-group on the free electron pair present on the ring nitrogen and available for oxide formation. Similar difficulties were experienced with the dinitrophenylphenanthridines. Although 3-*nitro*-9-p-*nitrophenylphenanthridine* N-*oxide* was obtained from the corresponding dinitro-compound in low yield, all attempts to prepare 2 : 7-dinitro-9-phenylphenanthridine *N*-oxide for conversion into the Dimidium bromide analogue were unsuccessful.

Reduction of the nitro-9-phenylphenanthridine *N*-oxides with stannous chloride in hydrochloric acid solution furnished the corresponding *amino*-9-*phenylphenanthridine* N-*oxides*. Reduction of 3-nitro-9-*p*-nitrophenylphenanthridine *N*-oxide, on the other hand, invariably resulted in loss of the oxido-grouping and formation of 3-amino-9-*p*-aminophenylphenanthridine. Limited success attended efforts at the direct oxidation of 3-*diacetylamino*-9-p-*diacetylaminophenylphenanthridine*, wherein the corresponding N-*oxide* was obtained in very low yield. Attempts to extend this reaction to 7-*diacetylamino*-9-p-*diacetylaminophenyl*-, 2 : 7-*bisdiacetylamino*-9-*phenyl*-, and 2 : 7-dicarbethoxyamino-9-phenyl-phenanthridine proved unsuccessful, however, and further work on the " *N*-oxide " analogue of Dimidium bromide (II) was abandoned.

9-4′-*Pyridylphenanthridine*, prepared by ring closure of 2 : 4′-*picolinamidodiphenyl*, formed a homogeneous *monoxide* on treatment with 1·1 equivalents of perphthalic acid. The constitution of a 9-4′-*pyridylphenanthridine* 1′-*oxide* has been assigned to this compound from analogy with related work on the monoquaternation of 9-3′-pyridylphenanthridine (Petrow and Wragg, *J.*, 1947, 1410) and on general theoretical grounds. Reaction with excess of perphthalic acid led to the formation of the corresponding *dioxide*. Attempts to convert 9-(5-*nitro*-2-*furyl*)*phenanthridine* into its oxide were unsuccessful.

The reaction of phenanthridine *N*-oxide with phosphorus oxychloride followed the pattern established for similar compounds (see, *e.g.*, Baxter, Newbold, and Spring, *J.*, 1948, 1859), 9-chlorophenanthridine being formed. When 9-phenylphenanthridine *N*-oxide was treated in the same way, however, a *chloro*-9-*phenylphenanthridine* was obtained, identical with authentic 3-*chloro*-9-*phenylphenanthridine* prepared by the Sandmeyer reaction from the corresponding amino-compound. When 9-methylphenanthridine *N*-oxide was treated with phosphorus oxychloride, two halogenated products were obtained. One of these was identified with 9-chloromethylphenanthridine previously described by Morgan and Walls (*J.*, 1931, 2447). The other product has, by analogy with its phenyl analogue, been assigned the constitution of a 3-*chloro*-9-*methylphenanthridine*.

EXPERIMENTAL.

(M. p.s are uncorrected. Microanalyses are by the Analytical Department, The British Drug Houses Ltd., and by Drs. Weiler and Strauss, Oxford.)

Substituted 2-Benzamidodiphenyls.—The acid chloride (0·1 mol.) (prepared from the acid and thionyl chloride) was added in portions to a solution of 2-aminodiphenyl (0·1 mol.) in pyridine (15—20 ml.), and the mixture heated on the steam-bath for 2 hours to complete the reaction. Addition of dilute hydrochloric acid usually precipitated the amide as a solid, which was collected, washed, and crystallised from alcohol or alcohol–light petroleum. Occasionally, preliminary vacuum-distillation was required before the amide could be obtained as a solid. The compounds listed in Table I were thus prepared. The yields are based on the acid used.

5-Carbethoxyamino-2-acetamidodiphenyl, prepared by reduction of 5-nitro-2-acetamidodiphenyl followed by carbethoxylation, formed small pale-cream needles, m. p. 127—128° (77%) (Found : C, 68·4; H, 6·0. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1%), from benzene–light petroleum.

4′-Carbethoxy-2-acetamidodiphenyl, prepared as for the foregoing compound, formed (91%) silvery leaflets, m. p. 160—161° (cf. Walls, *J.*, 1947, 67).

2-*Nitro*-4 : 4′-*dibenzamidodiphenyl.*—2-Nitrobenzidine (23·6 g.) in warm pyridine (30 ml.) was treated with benzoyl chloride (30 g.) in portions. After 30 minutes on the water-bath the *product* was isolated and purified from pyridine–light petroleum, to give pale yellow prisms, m. p. 290—291° (Found : C, 71·7; H, 4·5. $C_{26}H_{19}O_4N_3$ requires C, 71·4; H, 4·4%), in nearly quantitative yield.

2-*Amino*-4 : 4′-*dibenzamidodiphenyl.*—Finely powdered 2-nitro-4 : 4′-dibenzamidodiphenyl (16·7 g.) was stirred with concentrated hydrochloric acid (83 ml.) containing a little alcohol to prevent frothing, and a solution of stannous chloride (47 g.) in concentrated hydrochloric acid (50 ml.) added. After 2 hours on the water-bath the mixture was poured, with stirring, into excess of sodium hydroxide solution (30%), and the precipitated solids extracted with boiling pyridine. Evaporation of the extract under reduced pressure, followed by crystallisation of the residue (12·0 g.; m. p. 255—258°) from aqueous pyridine, gave 2-*amino*-4 : 4′-*dibenzamidodiphenyl*, buff-coloured prisms, m. p 270° (Found : C, 76·9; H, 5·2. $C_{26}H_{21}O_2N_3$ requires C, 76·7; H, 5·2%).

4 : 4′-*Dicarbethoxyamino-2-dimethylaminodiphenyl.*—A well-stirred solution of 2-amino-4 : 4′-dicarbethoxyaminodiphenyl (13 g.) in water (50 ml.) at 80° was treated in portions with aqueous sodium hydroxide (19 g. in 28 ml. of water) and methyl sulphate (35 g.), added alternately so that the mixture remained alkaline. After a further 30 minutes' heating, the product was collected, heated with acetic anhydride (20 ml.) for 10 minutes on the water-bath, and poured into dilute sulphuric acid (20 ml. acid in 300 ml. of water), and the mixture was filtered while hot. The filtrate was made alkaline, giving 4 : 4′-*dicarbethoxyamino-2-dimethylaminodiphenyl*, prismatic needles (6·7 g.), m. p. 171—172° (Found : C, 63·7; H, 7·5. $C_{20}H_{25}O_4N_3,C_2H_6O$ requires C, 63·3; H, 7·5%), from ethanol.

2-*Benzamido-4′-chlorosulphonyldiphenyl.*—2-Benzamidodiphenyl (21·2 g.) was added in portions with stirring to chlorosulphonic acid (42·4 g.) at 10°. The mixture was then heated at 60° for 2 hours and, after cooling, poured on ice. The sticky product was dissolved in chloroform and precipitated with light petroleum, giving 2-*benzamido-4′-chlorosulphonyldiphenyl*, needles (12·2 g.), m. p. 162—163° (Found : C, 62·1; H, 3·9; Cl, 9·9. $C_{19}H_{14}O_3ClNS$ requires C, 61·4; H, 3·8; Cl, 9·5%), from benzene (cf. B.PP. 597,809, 597,810 for orientation).

2-*Benzamido-4′-2″-pyridylsulphamyldiphenyl*, prepared from the above compound, formed prisms m. p. 223°, from ethoxyethyl alcohol (Found : C, 66·5; H, 4·8. $C_{24}H_{19}O_3N_3S$ requires C, 67·1; H, 4·5%). The p-*chlorophenylsulphamyl* derivative separated from ethoxyethyl alcohol in small leaflets, m. p. 239° (Found : C, 64·9; H, 4·5. $C_{25}H_{19}O_3N_2SCl$ requires C, 64·9; H, 4·1%). The *sulphonomorpholide* formed needles, m. p. 161—163° (Found : C, 65·3; H, 5·3. $C_{23}H_{22}O_4N_2S$ requires C, 65·4; H, 5·3%), from aqueous ethoxyethyl alcohol. The *sulphonopiperidide* formed needles, m. p. 102—104° (Found : N, 6·6. $C_{24}H_{24}O_3N_2S$ requires N, 6·7%), from ethanol.

The p-*nitrophenylsulphamyl* derivative formed pale yellow leaflets, m. p. 247° (Found : C, 63·3; H, 3·8. $C_{25}H_{19}O_5N_3S$ requires C, 63·4; H, 4·0%), from ethoxyethyl alcohol.

2-iso*Nicotinamidodiphenyl.*—*iso*Nicotinic acid (30 g.), prepared (56% yield) by the method of Linnell and Vyas (*Quart. J. Pharm.*, 1947, **20**, 120), was heated under reflux with thionyl chloride (85 ml.) for 6 hours. Unchanged thionyl chloride was removed under reduced pressure, and the residue evaporated with benzene. The *iso*nicotinoyl chloride hydrochloride in gently refluxing chlorobenzene (320 ml.) was treated in portions with 2-aminodiphenyl (40 g.) in chlorobenzene (85 ml.). Heating was continued for a further 30 minutes, and the mixture was cooled, the chlorobenzene decanted off, and the semi-solid residue washed by decantation with ether. The product was dissolved in hot methyl alcohol (*ca.* 400 ml.), the base (42·5 g.; m. p. 107—111°) precipitated with aqueous ammonia, and the mixture cooled. 2-iso*Nicotinamidodiphenyl* formed needles, m. p. 113·5° (Found : C, 79·0; H, 5·3. $C_{18}H_{14}ON_2$ requires C, 78·8; H, 5·1%), from aqueous methanol.

The compounds listed in Table II were prepared in a similar way.

4′-Chloro-2-benzamidodiphenyl.—The method of Bradshaw and Wissow (*J. Amer. Chem. Soc.*, 1946, **68**, 405) was modified as follows : 4′-Chloro-2-nitrodiphenyl (11·2 g.), ethanol (45 ml.), water (12 ml.), reduced iron (15 g.), and a few drops of concentrated hydrochloric acid were heated under reflux on the water-bath for 1 hour. The mixture was then made just alkaline with aqueous ammonia and filtered hot. Extraction of the solids with hot ethanol gave an oil from which 4′-chloro-2-benzamidodiphenyl was obtained, on benzoylation, as needles (10·6 g.), m. p. 167—169°, from ethanol.

5-Chloro-2-acetamidodiphenyl.—The following improved method was used : 2-acetamidodiphenyl (10·6 g.) and fused sodium acetate (12·3 g.) in glacial acetic acid (45 ml.) on the water-bath were treated with a stream of chlorine until 3·5 g. had been absorbed. Heating was continued for a further 30 minutes and the mixture was then diluted with water and extracted with chloroform. The product was distilled under reduced pressure, the fraction, b. p. 170—200°/0·05 mm., yielding 5-chloro-2-acetamidodiphenyl, m. p. 120—121° (Found : C, 68·9; H, 5·0. Calc. for $C_{14}H_{12}ONCl$: C, 68·4; H, 4·9%), on crystallisation from alcohol–light petroleum (cf. Scarborough and Waters, *J.*, 1927, 93).

TABLE I.

Substituted diphenyls.

Substituent.	M. p. or b. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Reqd., %. C.	Reqd., %. H.	Reqd., %. N.	Description.*
2-o-*Methylbenzamido-*	88—89° b. p. 185 (0·05 mm.)	52	$C_{20}H_{17}ON$	83·1	5·6	—	83·4	6·0	—	Needles
2-m-*Methylbenzamido-*	89—90 b. p. 180 (0·08 mm.)	63	,,	83·5	6·0	—	83·4	6·0	—	Needles
2-p-*Methylbenzamido-*	107—108	66	,,	83·9	5·8	4·7	83·4	6·0	4·9	Needles
2-o-*Chlorobenzamido-*	103	58	$C_{19}H_{14}ONCl$	73·9	4·5	^{e}	74·2	4·3	^{e}	Needles ^{b}
2-m-*Chlorobenzamido-*	107—108	67	,,	74·2	4·6	—	74·2	4·3	—	Wispy needles
2-p-*Chlorobenzamido-*	104	64	,,	73·6	4·5	—	74·2	4·3	—	Wispy needles
5-*Nitro-2-benzamido-*	148—149	80	$C_{19}H_{14}O_3N_2$	71·1	4·3	—	71·7	4·4	—	Flat yellow needles ^{b}
2-o-*Anisamido-*	162	40	$C_{20}H_{17}O_2N$	79·1	5·6	—	79·2	5·7	—	Flat needles ^{a}
2-m-*Anisamido-*	76—77	58	,,	79·2	5·7	—	79·2	5·7	—	Needles ^{a}
2-(2 : 5-*Dimethoxybenzamido*)-	134—135	68	$C_{21}H_{19}O_3N$	75·8	5·6	—	75·7	5·8	—	Leaflets
2-(3 : 4-*Dimethoxybenzamido*)-	128—130	73	,,	76·0	5·8	4·1	75·7	5·8	4·2	Small needles ^{c}
2-p-iso*Propoxybenzamido-*	150 (softens 115)	69	$C_{22}H_{21}O_2N$	79·8	6·4	—	79·7	6·4	—	Wispy needles ^{c}
2-(p-n-*Propoxybenzamido*)-	116—118	49	,,	79·6	6·5	—	79·7	6·4	—	Long needles
2-(3-*Methoxy-4-ethoxybenzamido*)-	111 b. p. 223 (0·07 mm.)	58	$C_{22}H_{21}O_3N$	76·2	6·3	—	76·1	6·1	—	Needles
2-(3-*Methoxy-4-*iso*propoxybenzamido*)-	148·5	73	$C_{23}H_{23}O_3N$	—	—	3·9	—	—	3·9	Needles
2-(3 : 4-*Methylenedioxybenzamido*)-	145—146	66	$C_{20}H_{15}O_3N$	75·6	4·7	—	75·7	4·8	—	Needles
2 : 4 : 4'-*Tribenzamido-*	285	59	$C_{33}H_{25}O_3N_3$	77·2	4·5	—	77·5	4·9	—	Micro-prisms ^{d}
2-2'-*Furamido-*	76—77·5	71	$C_{17}H_{13}O_2N$	77·0	5·2	—	77·6	5·0	—	Needles
2-(5-*Nitro-2-furamido*)-	134—135	55	$C_{17}H_{12}O_4N_2$	65·7	4·1	—	66·2	3·9	—	Yellow leaflets
4'-*Carbethoxyamino-2-(5-nitro-2-furamido*)-	179—180	50	$C_{20}H_{17}O_6N_3$	60·8	4·4	—	60·8	4·3	—	Flat needles ^{b}

* Recrystallised from : ^{a} light petroleum, ^{b} ethoxyethyl alcohol, ^{c} benzene, ^{d} pyridine. ^{e} Found : Cl, 11·4. Reqd. : Cl, 11·5%.

TABLE II.

Substituted diphenyls.

Substituent.	M. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Reqd., %. C.	Reqd., %. H.	Reqd., %. N.	Description.*
2-*Picolinamido-*	100°	82	$C_{18}H_{14}ON_2$	78·3	5·3	—	78·8	5·1	—	Large buff needles ^{a}
4'-*Nitro-2-picolinamido-*	215—217	75	$C_{18}H_{13}O_3N_2$	67·3	4·0	—	67·7	4·1	—	Wispy yellow needles ^{b}
4'-*Nitro-2-*isonicotinamido-	185—186	85	,,	67·1	4·1	—	67·7	4·1	—	Wispy yellow needles ^{c}
5-*Nitro-2-picolinamido-*	207—208	61	,,	67·8	4·1	—	67·7	4·1	—	Needles ^{b}
5-*Nitro-2-*isonicotinamido-	138	63	,,	67·8	4·1	—	67·7	4·1	—	Buff prisms ^{d}
4'-*Carbethoxyamino-2-picolinamido-*	181—182 (softens 158)	68	$C_{21}H_{19}O_3N_3,C_6H_6$	73·0	5·6	—	73·8	5·7	—	Needles ^{e}
2-(2-*Phenyl-4-quinolylamido*)-	173	76	$C_{28}H_{20}ON_2$	81·9	4·9	6·8	81·9	5·0	6·9	Prisms ^{f}
5-*Nitro-2-(2-phenyl-4-quinolylamido*)-	228	72	$C_{28}H_{19}O_3N_3$	75·1	4·5	—	75·5	4·3	—	Prisms ^{g}
4'-*Nitro-2-(2-phenyl-4-quinolylamido*)-	223	83	,,	75·5	4·5	—	75·4	4·3	—	Small needles ^{h}
4'-*Carbethoxyamino-2-(2-phenyl-4-quinolylamido*)-	195	81	$C_{31}H_{25}O_3N_3$	76·2	4·9	—	76·4	5·2	—	Flat buff needles ^{c}
2-(2-o-*Chlorophenyl-5 : 6-benz-4-quinolylamido*)-	234—236	70	$C_{32}H_{21}ONCl$	79·0	4·7	—	79·3	4·4	—	Cream needles ^{b}

* Recrystallised from : ^{a} light petroleum, ^{b} ethoxyethyl alcohol, ^{c} methanol, ^{d} benzene–light petroleum, ^{e} benzene, ^{f} acetone, ^{g} nitrobenzene–ether, ^{h} nitrobenzene.

2-(p-*Aminobenzamido*)*diphenyl*, prepared by reduction of the corresponding nitro-compound with reduced iron, separated (87%) from ethanol in cubes, m. p. 144—145° (Found: C, 79·3; H, 5·7; N, 9·5. $C_{19}H_{16}ON_2$ requires C, 79·1; H, 5·6; N, 9·7%). It was converted into 2-(p-*carbethoxyaminobenzamido*)-*diphenyl*, needles, m. p. 166—167° (Found: C, 73·7; H, 6·0. $C_{22}H_{20}O_3N_2$ requires C, 73·3; H, 5·6%), from ethanol, by the method of Lesslie and Turner (*J.*, 1943, 1588).

9-*Subsituted Phenanthridines.*—The amidodiphenyl (1 part), phosphorus oxychloride (2 parts), and nitrobenzene (3 parts) were heated under reflux in an oil-bath for 1½—2½ hours. The reaction mixture was poured on excess of ice–sodium hydroxide solution, and the nitrobenzene removed in steam. After cooling, the separated solids were collected, washed, and purified by crystallisation. The compounds listed in Table III were thus prepared.

9-4′-*Pyridylphenanthridine dihydrochloride* formed yellow prisms, m. p. 235° (decomp.) (Found: C, 65·3; H, 4·4. $C_{18}H_{12}N_2,2HCl$ requires C, 65·7; H, 4·3%), from ethanol.

3-*Chloro*-9-*phenylphenanthridine.*—3-Amino-9-phenylphenanthridine (5·0 g.), dissolved in concentrated hydrochloric acid (7 ml.) and water (3 ml.), was diazotised at 0° with sodium nitrite (1·4 g.) dissolved in a little water. The diazonium solution was then rapidly added to cuprous chloride solution [prepared from cupric sulphate (6·2 g.), sodium chloride (1·75 g.), and water (20 ml.; saturated with SO_2), the resulting cuprous chloride being dissolved in hydrochloric acid (12 ml.)]. After being kept overnight, the precipitated solids were collected and extracted with sodium hydroxide solution, and the insoluble residue was crystallised from ethanol. 3-*Chloro*-9-*phenylphenanthridine* formed yellow leaflets (1·3 g.), m. p. 141—142° (Found: C, 79·0; H, 4·4. $C_{19}H_{12}NCl$ requires C, 78·7; H, 4·3%).

7-*Amino*-9-*phenylphenanthridine.*—Finely powdered 7-nitro-9-phenylphenanthridine (14·5 g.) was stirred with concentrated hydrochloric acid (60 ml.) while a solution of stannous chloride (40 g.) in hydrochloric acid (43 ml.) was added. After 3 hours on the water-bath the cooled mixture was filtered, the yellow stannichloride dissolved in water, and the solution basified. Hot ethoxyethyl alcohol extracted 7-*amino*-9-*phenylphenanthridine*, yellow needles (10·8 g.), m. p. 168° (Found: C, 83·8; H, 5·3. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2%), from ethanol.

3-*Amino*-9-m-*aminophenylphenanthridine*, prepared similarly to the foregoing compound, formed yellow prisms (63%), m. p. 201° (Found: C, 79·5; H, 5·1. $C_{19}H_{15}N_3$ requires C, 80·0; H, 5·3%), from ethanol.

7-*Amino*-9-m-*aminophenylphenanthridine*, prepared similarly to the above compound, formed yellow prismatic needles (64%), m. p. 210° (Found: C, 79·4; H, 5·2. $C_{19}H_{15}N_3$ requires C, 80·0; H, 5·3%), from ethoxyethyl alcohol. The NN′-*diacetyl* derivative formed needles, m. p. >290° (Found: C, 74·5; H, 5·0; N, 11·1. $C_{23}H_{17}O_2N_3$ requires C, 75·2; H, 4·7; N, 11·4%), from alcohol.

5-*Amino*-9-*phenylphenanthridine*, prepared by ring closure of 2 : 2′-dibenzamidodiphenyl (3 g.) with phosphorus oxychloride (6 g.) and nitrobenzene (9 ml.) at 160° for 2 hours, formed yellow prisms, m. p. 164° (Found: C, 84·1; H, 5·3; N, 10·4. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%), from aqueous ethanol. The *monohydrochloride* formed yellow needles, m. p. 335—338° (decomp.) (Found: C, 74·3; H, 4·9; N, 8·6. $C_{19}H_{14}N_2,HCl$ requires C, 74·4; H, 4·9; N, 9·1%), from aqueous alcohol.

9-p-*Diacetylaminophenylphenanthridine.*—9-*p*-Aminophenylphenanthridine (5 g.), acetic anhydride (50 ml.), and one drop of concentrated sulphuric acid were heated under reflux for 4 hours. Excess of acetic anhydride was removed under reduced pressure leaving 9-p-*diacetylaminophenylphenanthridine*, m. p. 207° (Found: C, 78·4; H, 5·3. $C_{23}H_{18}O_2N_2$ requires C, 77·9; H, 5·1%) after crystallisation.

3-*Diacetylamino*-9-p-*diacetylaminophenylphenanthridine* crystallised from ethoxyethyl alcohol–ethanol (1 : 2) in needles, m. p. 221—222° (softening at 217°) (Found: C, 71·0; H, 5·3. $C_{27}H_{23}O_4N_3$ requires C, 71·5; H, 5·1%).

7-*Diacetylamino*-9-p-*diacetylaminophenylphenanthridine* formed small prisms, m. p. 227—229° (Found: C, 71·0; H, 5·1. $C_{27}H_{23}O_4N_3$ requires C, 71·5; H, 5·1%), from aqueous ethanol.

3-*Carbethoxyamino*-9-*methylphenanthridine*, pale yellow prisms (3 g.) from benzene, m. p. 177—179° (Found: C, 72·7; H, 5·8. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·8%), was obtained by ring closure of 5-carbethoxy-2-acetamidodiphenyl (5·0 g.) with phosphorus oxychloride (10 ml.) under reflux for 45 minutes.

9-p-*Hydroxyphenylphenanthridine.*—9-*p*-Aminophenylphenanthridine (2·0 g.) in 2N-sulphuric acid (20 ml.) was heated on the water-bath and then cooled to 0°. Sodium nitrite (0·8 g.), dissolved in a little water, was then added, and the diazotised solution poured into water (50 ml.) at 70°. After being kept overnight, the solids were collected, purified by solution in alkali, and crystallised from ethanol. 9-p-*Hydroxyphenylphenanthridine* formed prismatic needles (1·4 g.), m. p. 237° (Found: C, 83·7; H, 4·8. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%).

9-m-*Hydroxyphenylphenanthridine*, prepared similarly, formed buff-coloured microneedles, m. p. 225—226° (Found: C, 83·7; H, 4·8. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%), from aqueous ethanol.

9-*Morpholinomethylphenanthridine.*—9-Chloromethylphenanthridine (6·3 g.), morpholine (8·5 g.), alcohol (25 ml.), and chloroform (5 ml.) were heated under reflux for 2 hours. Water was added, the mixture extracted with chloroform and concentrated to small bulk, and light petroleum added. 9-*Morpholinomethylphenanthridine* separated and was obtained as yellow prisms, m. p. 95° (Found: C, 77·6; H, 6·7. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5%), from light petroleum.

9-(5-*Nitro*-2-*furyl*)*phenanthridine*, yellow needles, m. p. 187° (Found: C, 69·6; H, 3·5. $C_{17}H_{10}O_3N_2$ requires C, 70·3; H, 3·5%), from acetone, was obtained (36%) by heating 2-(5-nitro-2-furamido)-diphenyl (5·0 g.) with phosphorus oxychloride (10 ml.) and nitrobenzene (15 ml.) for 30 minutes at 180°.

9-p-*Diguanidophenylphenanthridine.*—9-*p*-Aminophenylphenanthridine (2·65 g.), dicyandiamide (2·7 g.), water (15 c.c.), and hydrochloric acid (1 c.c.) were heated under reflux for 3 hours. The mixture was basified with ammonia, and the solid collected and crystallised from ethanol, from which it separated as needles (1·0 g.) (Found, in a sample dried at 100°/30 mm.: C, 69·2; H, 5·2; N, 23·0. $C_{21}H_{18}N_6,\frac{1}{2}H_2O$ requires C, 69·4; H, 5·3; N, 23·1%).

7-*Diguanido*-9-*phenylphenanthridine monohydrate*, similarly prepared, formed prismatic needles, m. p. 153° (decomp.) (Found: C, 68·0; H, 5·7; N, 22·4. $C_{21}H_{18}N_6,H_2O$ requires C, 67·7; H, 5·4; N, 22·5%), from alcohol. The *picrate* formed small yellow prisms, m. p. 235° (decomp.) (Found: N, 20·6. $C_{21}H_{18}N_6,C_6H_3O_7N_3$ requires N, 21·6%), from ethoxyethyl alcohol.

TABLE III.

9-Substituted phenanthridines.

Substituent.	M. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Reqd., %. C.	Reqd., %. H.	Reqd., %. N.	Description.*
m-*Tolyl-*	98—99°	78	$C_{20}H_{15}N$	89·6	5·9	—	89·2	5·6	—	Prismatic needles [a]
p-*Tolyl-*	108	73	,,	88·8	5·6	—	89·2	5·6	—	Needles [a], (1)
7-Chloro-9-phenyl-	120	57	$C_{19}H_{12}NCl$	78·6	4·3	—	78·7	4·3	—	Cream needles [b]
o-*Chlorophenyl-*	125	94	,,	78·5	4·0	—	78·7	4·3	—	Prisms [b]
m-*Chlorophenyl-*	137—138	87	,,	78·5	4·1	—	78·7	4·3	—	Silver needles [c]
p-*Chlorophenyl-*	157·5	84	,,	79·2	4·2	—	78·7	4·3	—	Silver needles [b]
3-Nitro-9-phenyl-	228—229	96	$C_{19}H_{12}O_2N_2$	75·5	4·0	—	76·0	4·0	—	Pale yellow wispy needles [d], (2)
2 : *7-Dibenzamido-9-phenyl-*	321—322	89	$C_{33}H_{23}O_2N_3$	79·6	4·8	8·1	80·3	4·7	8·5	Pale cream micro-needles [e], (3)
o-*Methoxyphenyl-*	127	75	$C_{20}H_{15}ON$	84·2	5·3	5·0	84·2	5·3	4·9	Needles [f]
m-*Methoxyphenyl-*	128—129	89	,,	84·2	5·3	—	84·2	5·3	—	Prisms [f]
p-*Methoxyphenyl-*	146	80	,,	83·7	4·8	—	84·2	5·3	—	Needles [f]
2′-Methoxy-5′-bromophenyl-	148	77	$C_{20}H_{14}ONBr$	65·8	3·9	—	66·0	3·9	—	Cubes [f]
p-*Ethoxyphenyl-*	149—150	64	$C_{21}H_{17}ON$	84·0	5·9	4·8	84·2	5·7	4·7	Flat needles [f]
2′ : *5′-Dimethoxyphenyl-*	163	95	$C_{21}H_{17}O_2N$	80·0	5·4	—	80·0	5·4	—	Prisms [f]
3′ : *4′-Dimethoxyphenyl-*	169	88	,,	79·6	5·3	—	80·0	5·4	—	Prismatic needles [f]
3′ : *4′-Methylenedioxyphenyl-*	113	70	$C_{20}H_{13}O_2N$	79·8	4·4	4·3	80·4	4·4	4·7	Needles [f]
p-n-*Propoxyphenyl-*	116—117	96	$C_{21}H_{17}O_2N$	—	—	4·1	—	—	4·5	Cream needles [f]
p-iso*Propoxyphenyl-*	118—119	62	,,	91·0	5·8	—	90·3	6·1	—	Needles [f]
3′-Methoxy-4′-ethoxyphenyl-	118—120	53	$C_{22}H_{19}O_2N$	—	—	4·7	—	—	4·3	Needles [f]
*3′-Methoxy-4′-*iso*propoxyphenyl-*	137—139	86	$C_{22}H_{21}O_2N$	80·4	5·8	—	80·4	6·2	—	Needles [f]
*3′-Methoxy-4′-*n-*propoxyphenyl-*	128—129	77	,,	79·8	6·2	—	80·4	6·2	—	Needles [f]
4′-Pyridyl-	160	74	$C_{18}H_{12}N_2$	84·2	4·8	—	84·4	4·7	—	Prismatic needles [g], (4)
4′-Pyridyl- dihydrochloride	235 (decomp.)	—	$C_{18}H_{12}N_2,2HCl$	65·3	4·4	—	65·7	4·3	—	Yellow prisms [f]
2′-Phenyl-4′-quinolyl-	183—184	63	$C_{28}H_{18}N_2$	87·5	4·8	—	87·9	4·7	—	Pale cream prisms [f], (5)
3-Nitro-9-(2-phenyl-4-quinolyl)-	>295	70	$C_{28}H_{17}O_2N_3$	79·0	4·1	—	78·7	4·0	—	Small needles [d], (5)
7-Nitro-9-(2-phenyl-4-quinolyl)-	282	58	$C_{28}H_{17}O_2N_3$	78·2	3·8	—	78·7	4·0	—	Pale yellow needles [d], (5)
9-(2-o-*Chlorophenyl-5 : 6-benz-4-quinolyl-*)	260	65	$C_{32}H_{19}NCl$	82·3	4·1	6·0	81·6	3·9	5·3	Leaflets [h]

(1) Since completion of this preparation Gilman and Nelson (*J. Amer. Chem. Soc.*, 1948, **70**, 3316) have described an alternative preparation from phenanthridine and tolyl-lithium.

Periods of refluxing: (2) 16 hours, (3) 3½ hours, (4) 16 hours, (5) 18 hours.

* Recrystallised from: [a] light petroleum, [b] methanol, [c] acetone, [d] nitrobenzene, [e] aq. pyridine, [f] ethanol, [g] acetone–ethanol, [h] ethoxyethyl alcohol.

Phenanthridine 10-*Oxide.*—Phenanthridine (18·1 g.), dissolved in a little chloroform, was added to ethereal perphthalic acid solution (≡ 2·1 g. of active oxygen). After five days at 5° the solids were collected, ground with aqueous 5% ammonium hydroxide, and crystallised from ethanol (87%). *Phenanthridine* 10-*oxide* formed (after drying at 100°/20 mm.) leaflets, m. p. 220° (softening at 215°) (Found: C, 79·5; H, 4·6. $C_{13}H_9ON$ requires C, 80·0; H, 4·7%).

9-*Methylphenanthridine* 10-*oxide hydrochloride* was obtained (89%) in small buff prisms, m. p. 190—192° (decomp.; after drying) (Found: C, 68·1; H, 4·8. $C_{14}H_{12}ONCl$ requires C, 68·4; H, 4·9%).

9-*Ethylphenanthridine* 10-*oxide monohydrate* separated from aqueous acetic acid in pale pink needles, m. p. 252—253° (decomp.) (Found: C, 73·9; H, 6·3. $C_{15}H_{13}ON,H_2O$ requires C, 74·6; H, 6·3%).

9-*Phenylphenanthridine* 10-*Oxide.*—To a peracetic acid solution, prepared by heating 30% hydrogen peroxide (30 g.) and glacial acetic acid (50 g.) at 85° for one hour, was added 9-phenylphenanthridine (5·0 g.), and heating at 85° continued for a further 4—5 hours. The mixture was then poured into water, and the precipitated solids were collected and crystallised from chloroform. 9-*Phenylphenanthridine* 10-*oxide* was obtained (91%) in glistening buff leaflets, m. p. 212—215° (Found: C, 84·4; H, 5·0. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%).

The compounds listed in Table IV were thus prepared.

9-p-*Aminophenylphenanthridine* 10-*Oxide.*—Finely powdered 9-*p*-nitrophenylphenanthridine 10-oxide (4·9 g.) was stirred with hydrochloric acid (25 ml.) on a steam-bath, a few drops of ethanol being added to prevent frothing. Stannous chloride (14 g.) in hydrochloric acid (15 ml.) was then added; the suspended solids dissolved and were replaced, after 30 minutes' heating, by yellow crystals. After cooling to 5° the separated stannichloride was collected and decomposed with 10% aqueous sodium hydroxide, and the liberated base crystallised from ethanol. 9-p-*Aminophenylphenanthridine* 10-*oxide monohydrate* separated (40%) in yellow needles, m. p. 264—265° (decomp.) (Found: C, 75·2; H, 5·3. $C_{19}H_{14}ON_2,H_2O$ requires C, 75·0; H, 5·3%). The product is readily soluble in dilute acid and gives a positive primary amine test on diazotisation and coupling with alkaline 2-naphthol. For analysis the compound was dried at room temperature, as appreciable decomposition occurs at 100°.

9-m-*Aminophenylphenanthridine* 10-*oxide hemihydrate* formed yellow needles, m. p. 124—125° (decomp.) (Found: C, 77·8; H, 5·1; N, 9·0. $C_{19}H_{14}ON_2,\frac{1}{2}H_2O$ requires C, 77·3; H, 5·1; N, 9·5%), from ethanol.

3-*Amino*-9-*methylphenanthridine* 10-*oxide hemihydrate* was obtained (42%) in wispy yellow needles, m. p. 214° (Found: C, 72·3; H, 5·6. $C_{14}H_{12}ON_2,H_2O$ requires C, 72·1; H, 5·6%), from aqueous alcohol.

3-*Amino*-9-*phenylphenanthridine* 10-*oxide monohydrate* formed yellow needles (54%), m. p. 248° (decomp.) (Found: C, 75·5; H, 5·4. $C_{19}H_{14}ON_2,H_2O$ requires C, 75·0; H, 5·3%), from ethanol.

7-*Amino*-9-*phenylphenanthridine* 10-*oxide* separated (46%) in yellow needles, m. p. 278° (decomp.) (Found: C, 78·8; H, 5·3. $C_{19}H_{14}ON_2,\frac{1}{4}H_2O$ requires C, 78·6; H, 5·0%), from ethanol.

3-*Diacetylamino*-9-p-*diacetylaminophenylphenanthridine* 10-*oxide hemihydrate*, obtained in very low yield, separated from alcohol as an amorphous yellow powder, m. p. 268° (decomp., preheated bath) (Found: C, 67·7; H, 4·8. $C_{27}H_{23}O_4N_3,\frac{1}{2}H_2O$ requires C, 67·8; H, 5·1%).

9-4′-*Pyridylphenanthridine* 1′-*Oxide.*—The corresponding base was treated with 1·1 equivs. of perphthalic acid solution. After fractional crystallisation to remove unchanged material, the 1′-*oxide* was obtained in prismatic needles, m. p. 266° (Found: C, 79·4; H, 4·6; N, 10·0. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4; N, 10·3%), from aqueous ethanol.

9-4′-*Pyridylphenanthridine* 10 : 1′-*dioxide*, colourless prisms (71%), m. p. 303° (decomp.) (Found: C, 75·3; H, 4·2. $C_{18}H_{12}O_2N_2$ requires C, 75·0; H, 4·2%), from ethoxyethyl alcohol, was similarly obtained by using 3·3 equivs. of perphthalic acid.

Quaternary Salts.—The base was heated with methyl sulphate for 10 minutes in nitrobenzene at 160°. The methosulphate was isolated either by direct filtration or by removal of the nitrobenzene by steam-distillation followed by concentration under reduced pressure. The compounds listed in Table V were thus prepared.

3-*Amino*-9-(2-*phenyl*-4-*quinolyl*)*phenanthridine Dimethiodide.*—3-Nitro-9-(2-phenyl-4-quinolyl)phenanthridine dimethosulphate (1·0 g.), dissolved in concentrated hydrochloric acid (5 ml.), was treated with stannous chloride (3 g.) in hydrochloric acid (4 ml.) for 2 hours on the water-bath. After cooling, the orange-red stannichloride was collected and decomposed with hydrogen sulphide in dilute hydrochloric acid solution. The resulting dimethochloride proved very hygroscopic. The *dimethiodide* was therefore prepared, and formed orange-red needles (0·9 g.), m. p. 228° (decomp.) (Found: C, 51·5; H, 4·2. $C_{30}H_{25}N_3I_2,H_2O$ requires C, 51·5; H, 3·9%), from aqueous ethanol.

2 : 3-*Di*-2′-*furylquinoxaline.*—Furil (9·5 g.), in hot ethanol (100 ml.) and chloroform (70 ml.), was heated with *o*-phenylenediamine (5·4 g.) in ethanol (10 ml.) under reflux for 30 minutes. Concentration gave 2 : 3-*di*-2′-*furylquinoxaline*, yellow needles (12·6 g.), m. p. 130—131° (Found: C, 73·0; H, 3·4. $C_{16}H_{10}O_2N_2$ requires C, 73·3; H, 3·8%). Attempts to convert this compound into the *N*-oxide gave only 2 : 3-dihydroxyquinoxaline, white needles, m. p. >300° (Found: C, 59·0; H, 3·7. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7%), from water. Attempts to prepare quaternary salt were likewise unsuccessful.

2 : 3-*Dimethylquinoline*-4-*carboxylic acid* 1-*oxide*, prepared by using peracetic acid, formed glistening leaflets (25%), m. p. 229° (decomp.) (Found: C, 66·2; H, 5·1. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%), from ethanol.

2-*Phenylquinoline*-4-*carboxylic acid* 1-*oxide*, prepared similarly, formed pale yellow prisms (75%), m. p. 260° (decomp.) (Found: C, 71·7; H, 4·3. $C_{16}H_{11}O_3N$ requires C, 72·4; H, 4·2%).

2-*Methyl*-5 : 6-*benzquinoline* 1-*oxide*, prepared by treating 2-methyl-5 : 6-benzquinoline (10 g.) in glacial acetic acid (200 ml.) with hydrogen peroxide (50 ml. of 30%) at 50° for 24 hours, was obtained as the monohydrate, m. p. 87—89°, from which the oxide was obtained after drying, m. p. 128—129° (Found: C, 80·0; H, 5·8; N, 6·7. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·3; N, 6·7%).

The Action of Phosphorus Oxychloride on Some Phenanthridine N-*Oxides.*—*Phenanthridine* 10-*oxide.* The oxide (1·0 g.), in a flask cooled in ice–water was treated with phosphorus oxychloride (4·0 ml.) added dropwise with shaking. The mixture was then heated on the water-bath for 15 minutes, poured on

TABLE IV.

Phenanthridine 10-oxides.

Substituent.	M. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.	Description.*
9-p-*Tolyl-*	196—197°	50	$C_{20}H_{15}ON$	83·3	5·4	84·2	5·3	Buff needles [a]
9-o-*Chlorophenyl-*	200	91	$C_{19}H_{12}ONCl$	74·2	4·0	74·6	4·0	Buff leaflets [b]
9-p-*Chlorophenyl-*	252 (decomp.)	68	„	74·1	4·0	74·6	4·0	Cream leaflets [c]
3-*Chloro-9-phenyl-*	174—175	74	„	73·8	4·0	74·6	4·0	Pale yellow needles [d]
7-*Chloro-9-phenyl-*	218	66	„	74·5	4·2	74·6	4·0	Pale yellow prisms [d]
9-m-*Nitrophenyl-*	181	63	$C_{19}H_{12}O_3N_2$	71·5	3·8	72·1	3·8	Small buff needles [d]
9-p-*Nitrophenyl-*	242—245 (decomp.)	87	„ ,H_2O	68·5	4·1	68·3	4·2	Golden needles [e]
3-*Nitro-9-phenyl-*	231	47	„ ,H_2O	69·0	4·2	68·3	4·2	Yellow needles [c]
7-*Nitro-9-phenyl-*	269—271 (decomp.)	68	„	72·1	4·0	72·1	3·8	Yellow needles [e]
3-*Nitro-9*-m-*nitrophenyl-*	286	26	$C_{19}H_{11}O_5N_3$	63·4	3·3	63·2	3·1	Yellow needles [e] * †
3-*Nitro-9-methyl-*	>265	96	(Could not be purified owing to insolubility. Used direct.)					
9-p-*Methoxyphenyl-*	232—234 (decomp.)	50	$C_{20}H_{15}O_2N$	78·9	4·7	79·7	5·0	Cream needles [d]

* Recrystallised from : [a] ethyl acetate, [b] aq. ethanol, [c] aq. acetic acid [e] ethanol, [d] acetic acid.

† Period of heating, 16 hours.

TABLE V.

Phenanthridine quaternary salts.

Substituent.*	M. p.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.	Description.†
9-p-*Tolyl- M.S.*	191—192°	76	$C_{22}H_{21}O_4NS$	67·3	5·6	66·8	5·4	Needles [a]
9-p-*Tolyl- M.I.*	219—221 (decomp.)	76	$C_{21}H_{18}NI$	61·5	4·4	61·3	4·4	Yellow prisms [a]
9-o-*Chlorophenyl- M.I.*	207—208	60	$C_{20}H_{15}NClI$	55·9	3·7	55·7	3·5	Yellow prisms or red needles [b]
9-p-*Chlorophenyl- M.S.*	191—192	47	$C_{21}H_{18}O_4NSCl$	60·4	4·4	60·6	4·4	Needles [b]
9-(5-*Nitro-2-furyl*)- *M.S.*	210 (decomp.)	65	$C_{19}H_{16}O_7N_2S$	54·5	3·5	54·8	3·9	Yellow needles [b]
9-*Morpholinomethyl- M.S.*	206—207 (decomp.)	69	$C_{20}H_{24}O_5N_2S$	59·5	5·8	59·4	6·0	Needles [a]
9-*Morpholinomethyl- M.I.*	195 (decomp.)	69	$C_{19}H_{21}ON_2I$	54·8	5·5	54·3	5·0	Needles [c]
9-4′-*Pyridyl- M.S.*	171—174 (decomp.)	80	$C_{20}H_{18}O_4N_2S$	63·1	5·1	62·8	4·7	Cream leaflets [a]
9-4′-*Pyridyl- M.I.*	>290	57	$C_{19}H_{15}N_2I$	57·2	4·0	57·3	3·8	Yellow needles [c]
9-(2-*Phenyl-4-quinolyl*)- *di-M.S.*	230 (decomp.)	60	$C_{32}H_{30}O_8N_2S_2,2H_2O$	57·6	5·4	57·3	5·1	Yellow needles [a]
3-*Nitro-9-(2-phenyl-4-quinolyl*)- *di-M.S.*	260 (decomp.)	77	$C_{32}H_{29}O_{10}N_3S_2,2H_2O$	53·7	4·7	54·2	4·9	Yellow prisms [b]
7-*Nitro-9-(2-phenyl-4-quinolyl*)- *di-M.S.*	254—255 (decomp.)	70	$C_{32}H_{29}O_{10}N_3S_2$	56·3	4·4	56·5	4·3	Small yellow needles [b]

* M.I. = methiodide; M.S. = methosulphate.

† Recrystallised from : [a] ethanol–ether, [b] ethanol, [c] aqueous ethanol.

ice, and neutralised with sodium hydroxide. The product in light petroleum (50 ml. of b. p. 80—100°; charcoal) deposited a little phenanthridone on storage overnight; this was removed, and the filtrate chilled to −30°. 9-Chlorophenanthridine separated, needles (0·95 g.), m. p. 116·5° (Found : C, 73·1; H, 3·8. Calc. for $C_{13}H_8NCl$: C, 73·1; H, 3·8%), from light petroleum, not depressed in admixture with an authentic specimen.

9-Chlorophenanthridine (10 g.) in alcohol (50 ml.) was added to a solution of sodium (1·2 g.) in alcohol (50 ml.), and the mixture heated under reflux for 3 hours. The product, in light petroleum, was purified by passage through a column of alumina, giving 9-*ethoxyphenanthridine*, needles (2·5 g.), m. p. 60° (Found : C, 80·5; H, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9), from methanol. On reaction with peracetic acid it was converted into phenanthridone.

9-*Phenylphenanthridine* 10-*oxide*. The oxide (2·0 g.) in a flask cooled in ice-water, was treated dropwise with phosphorus oxychloride (8 ml.). When the vigorous reaction had subsided the mixture was heated on the water-bath for 1½ hours, and the product isolated as before. Repeated crystallisation from methanol gave 3-chloro-9-phenylphenanthridine, m. p. 141° (Found : C, 79·0; H, 4·2. Calc. for $C_{19}H_{12}NCl$: C, 78·7; H, 4·3%), not depressed in admixture with an authentic specimen.

9-*Methylphenanthridine* 10-*oxide*. The oxide hydrochloride (2·0 g.) was treated with phosphorus oxychloride (8 ml.) as before, and the mixture heated on the water-bath for 45 minutes. After decomposition with ice and basification with ammonia, the product was fractionated from ethanol, giving 9-chloromethylphenanthridine, m. p. 132° (Found : C, 74·2; H, 4·6. Calc. for $C_{14}H_{10}NCl$: C, 73·8; H, 4·4%), not depressed in admixture with an authentic specimen. The mother-liquors yielded (? 3-)*chloro*-9-*methylphenanthridine*, small needles, m. p. 91·5—92·5° (Found: C, 73·3; H, 4·6%), from light petroleum.

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143. 9 : 10-*Dihydrophenanthrenes. Part I. The Formation of 9* : 10-*Dihydrophenanthrene from* 2 : 2′-*Disubstituted Diphenyls.*

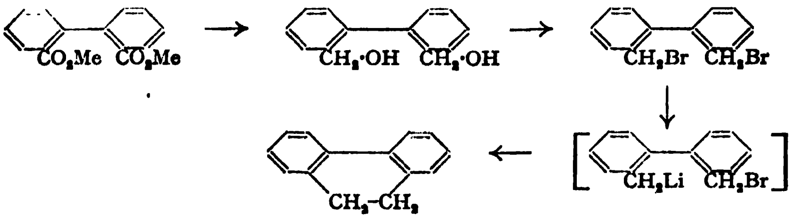
By D. Muriel Hall, Mary S. Lesslie, and E. E. Turner.

9 : 10-Dihydrophenanthrene is formed in high yield by the action of phenyl-lithium on 2 : 2′-di(bromomethyl)diphenyl, which is smoothly formed from the corresponding dihydroxy-compound. The latter is formed in almost quantitative yield by reducing alkyl diphenates with ethereal lithium aluminium hydride. Dihydrophenanthrene is formed in considerable quantities when the di(bromomethyl)diphenyl reacts with magnesium in the presence of ether.

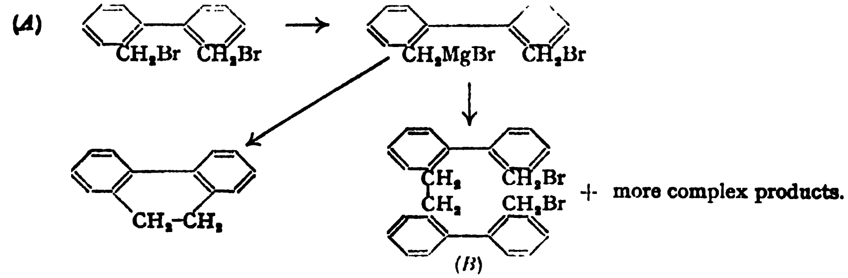
The most obvious routes to 9 : 10-dihydrophenanthrene are (*a*) the catalytic hydrogenation of phenanthrene and (*b*) the Wurtz–Fittig process from 2 : 2′-di(halogenomethyl)diphenyls. Burger and Mosettig (*J. Amer. Chem. Soc.*, 1935, **57**, 2731; 1936, **58**, 1857) obtained the hydrocarbon by the catalytic hydrogenation of phenanthrene, but the experimental conditions are beyond present resources. Dihydrophenanthrene must have been present in considerable quantities in the liquid product obtained by Kenner and Turner (*J.*, 1911, **99**, 2101) by the action of sodium on 2 : 2′-di(bromomethyl)diphenyl, since oxidation of the crude product gave a 26% yield of phenanthraquinone. Kenner and Turner were misled in their conclusions by the inaccurate work of Schmidt and Mezger (*Ber.*, 1907, **40**, 4240) who described 9 : 10-dihydrophenanthrene as a solid melting at 94—95°. Schroeter, Müller, and Huang (*Ber.*, 1929, **62**, 645) obtained 3 g. of dihydrophenanthrene, m. p. 34·5—35°, by the action of sodium on 25 g. of 2 : 2′-di(bromomethyl)diphenyl.

It is now found that although Kenner's conditions for the side-chain bromination of 2 : 2′-ditolyl cannot be materially improved, 2 : 2′-ditolyl can be obtained in 65% yield by heating *o*-iodotoluene with activated copper powder (Kleiderer and Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 4219), a suitable alternative route being the Krizewsky–Turner reaction (*J.*, 1919, **115**, 559; *J. Proc. Roy. Soc. N.S.W.*, 1920, **54**, 37) with *o*-bromotoluene, when a yield of not less than 35% of ditolyl is obtained. Curiously enough, cupric chloride reacts indifferently with *o*-tolylmagnesium iodide, the main product of an attempted Krizewsky–Turner reaction with the latter being toluene, representing non-reaction.

As already indicated (*Nature*, 1949, **163**, 537), a more practicable route to 9 : 10-dihydrophenanthrene is the reduction of methyl diphenate by means of lithium aluminium hydride to 2 : 2′-di(hydroxymethyl)diphenyl, followed by conversion of the latter into 2 : 2′-di(bromomethyl)diphenyl and the interaction of this bromo-compound with phenyl-lithium. In this way, a 70% yield of dihydrophenanthrene from methyl diphenate is readily obtained.



When an attempt is made to prepare a Grignard reagent from 2 : 2′-di(bromomethyl)diphenyl (*A*) a mixture is obtained, the annexed scheme suggesting a probable sequence of reactions:



In the presence of either 2·2 or 1·0 atomic proportions of magnesium, 40% of the product is dihydrophenanthrene, the remainder containing high-melting products of which the main component appears to be 1 : 2-di-(2′-bromomethyl-2-diphenylyl)ethane (*B*), hydrolysable to 1 : 2-*di*-(2′-*hydroxymethyl*-2-*diphenylyl*)*ethane*.

EXPERIMENTAL.

2 : 2′-*Ditolyl*.—(*a*) Activated copper bronze was heated in a bath kept at about 260° and *o*-iodotoluene (50 g.) added at infrequent intervals. Heating was continued until refluxing ceased (about 20 hours). The somewhat cooled mixture was extracted with boiling chlorobenzene, and the filtered extract distilled. No unchanged iodotoluene was found. The main portion boiled at 254—256° and was almost pure ditolyl (13·5 g., 65% yield). Some commercial samples of copper bronze were found to be without perceptible action on boiling iodotoluene, even after attempted activation.

(*b*) A solution of *o*-tolylmagnesium bromide was prepared from 171 g. (1 g.-mol.) of *o*-bromotoluene and 24·5 g. of magnesium, in *ca*. 800 c.c. of ether. Finely-ground anhydrous cupric chloride (170 g.; 1·25 g.-mols.) was gradually added and the resulting mixture boiled for an hour. Ice and then concentrated hydrochloric acid were added and later (to oxidise the cuprous salts and render subsequent operations easier) about one g.-mol. of ferric chloride (about 400 g. of the dodecahydrate) in concentrated aqueous solution. The two layers were separated and the aqueous layer extracted several times with ether. The combined ethereal extracts were washed with water and alkali and fractionally distilled in steam. Fractions were cooled to about 10°. Oils which solidified were filtered and were pure ditolyl, m. p. 18°. Other fractions were separated or extracted with ether, and the dried ether extracts distilled. High-boiling materials (above 190°) were steam-distilled and the fractions treated as before. From a series of such operations, 836 g. of bromotoluene gave 156 g. (35% yield) of ditolyl, m. p. 18°, the highest individual yield being 42%.

Bromination of 2 : 2′-*Ditolyl*.—Ditolyl (9 g., 1 g.-mol.) was heated at 125—130° in a current of dry nitrogen which had bubbled slowly through 5·5 c.c. of bromine (just over 2 g.-mols.). Bromination took several hours, after which the product was cooled, stirred with dry light petroleum (b. p. 60—80°), and crystallised from this solvent. The process was not noticeably accelerated or improved if a trace of benzoyl peroxide was present. In all, 153·5 g. of ditolyl were brominated and gave 125·5 g. of 2 : 2′-di(bromomethyl)diphenyl, m. p. 89—92° (yield, 44%). One further crystallisation from light petroleum gave 119 g. of pure dibromide, m. p. 91—93°.

2 : 2′-*Di*(*hydroxymethyl*)*diphenyl*.—A solution of 76 g. of methyl diphenate in 700 c.c. of dry ether was added as fast as refluxing permitted to a solution of 17 g. of lithium aluminium hydride (1·6 g.-mols.) in 600 c.c. of ether. Water and then dilute sulphuric acid were added and the mixture freed from ether by heating on a water-bath. After the mixture had cooled, the solid was filtered off, washed, and dried. The *hydroxymethyl* compound crystallised from benzene in needles, m. p. 112—113° (yield, 55 g., 91%) (Found: C, 77·9; H, 6·8. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

Similar reduction of ethyl diphenate gave a 93% yield of diol.

2 : 2′-*Di*(*bromomethyl*)*diphenyl*.—The dihydroxyditolyl (15 g.) was added gradually to 750 c.c. of 46% hydrobromic acid at 90° and the mixture then boiled for 20 minutes. On cooling, a crystalline meal was formed and this was filtered off. The solid was dried *in vacuo* and crystallised from light

petroleum (b. p. 60—80°). From three such operations 67 g. (94% yield) of pure dibromo-compound were obtained.

9 : 10-*Dihydrophenanthrene*.—Freshly made lithium wire (3 g.) were cut into a nitrogen-filled flask containing 150 c.c. of dry ether, and 32 g. of bromobenzene were then gradually added. When interaction was complete, a solution of 54 g. of dibromoditolyl in 450 c.c. of ether was added as fast as refluxing allowed. Ice and water were then introduced and the two layers separated. Distillation of the dried ethereal solution gave 24·5 g. (86% yield) of dihydrophenanthrene, b. p. 174°/17 mm. After one crystallisation from methyl alcohol the hydrocarbon had m. p. 35·0—35·5°.

Action of Magnesium on 2 : 2′-*Di*(*bromomethyl*)*diphenyl*.—(*a*) The dibromo-compound (17 g.) reacted in ethereal solution with 0·5 atomic proportion of magnesium which had previously been activated with ethyl bromide. A further 0·5 atomic proportion of magnesium was added and the mixture boiled for 2 hours. A violet colour appeared at one stage and later disappeared. A white solid separated. Water and dilute hydrochloric acid were added without cooling and the solid separated and dried (4·4 g.). Crystallisation from a mixture of *cyclo*hexanone and light petroleum (b. p. 100—120°) gave 1 : 2-*di*-(2′-*hydroxymethyl*-2-*diphenylyl*)*ethane*, micro-crystalline, m. p. 242—244°, darkening at 235° [Found: C, 84·7; H, 6·8%; *M* (cryoscopic, in camphor), 422. $C_{28}H_{26}O_2$ requires C, 85·25; H, 6·65%; *M*, 394·5]. The ethereal layer, after being dried and distilled, gave 3·5 g. of dihydrophenanthrene (40%).

(*b*) Dibromoditolyl (34 g.) reacted in ethereal solution with 0·5 atomic proportion of activated magnesium and after further addition of 0·5 atomic proportion of magnesium the mixture was boiled for 6 hours. The white solid which separated was filtered off, washed with 47% hydrobromic acid, and dried (5·4 g.). The mixture of bromo-compounds obtained could not be separated, but crystallisation from a moist mixture of *cyclo*hexanone and light petroleum (b. p. 100—120°) gave the diol (m. p. 242—244°). From the ethereal mother-liquor 7·2 g. of dihydrophenanthrene were obtained.

(*c*) An ethereal solution of 17 g. of dibromoditolyl was boiled for several hours with 2·64 g. (2·2 atomic proportions) of activated magnesium. As in (*a*) and (*b*) a violet colour appeared intermediately and a solid separated. The yield of dihydrophenanthrene was 40%.

Our thanks are due to Imperial Chemical Industries Ltd. for a grant and to Dr. V. A. Petrow, of the British Drug Houses Ltd., for a gift of diphenic esters.

University of London (Bedford College).

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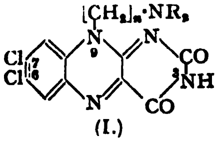
144. *A Series of 9-Dialkylaminoalkyl*iso*alloxazines.*

By R. B. Barlow and H. R. Ing.

A series of 6 : 7-dichloro-9-dialkylaminoalkyl*iso*alloxazines and some related compounds have been prepared and tested as antimalarial and trypanocidal agents.

Since 1945 numerous papers have appeared describing the preparation of *iso*alloxazine derivatives containing a basic side chain (Hall and Turner, *J.*, 1945, 699; Neeman, *J.*, 1946, 811; King and Acheson, *J.*, 1946, 681; 1948, 1926; Adams, Weisel, and Mosher, *J. Amer Chem. Soc.*, 1946, 68, 883; Kipnis, Weiner, and Spoerri, *ibid.*, 1947, 69, 799; Burkett, *ibid.*, 1947, 69, 2555; Hippchen, *Ber.*, 1947, 80, 263). When the work to be described herein was begun, in May 1944, it was proposed to prepare 6 : 7-dichloro*iso*alloxazines (I) with a basic side chain attached in the 9-position in the hope that they would prove to have antimalarial activity. It was known that mepacrine antagonized riboflavin in some micro-organisms and the 6 : 7-dichloro-compounds were chosen for the same reason as led Kuhn, Weygand, and Möller (*Ber.*, 1943, 76, 1044) to synthesise the 6 : 7-dichloro-analogue of riboflavin, although at the time this work of the German authors was unknown to us.



(I.)

The first compound to be prepared, 9-(3′-*piperidinopropyl*)-6 : 7-*dichloro*iso*alloxazine hydrochloride* (I; $n = 3$, $NR_2 = N{<}C_5H_{10}$), gave promise of being a member of an interesting new series; it was tested (serial number 5115) in the laboratories of Imperial Chemical Industries Ltd., and found by Dr. D. G. Davey to have definite antimalarial activity against *Plasmodium gallinaceum* in chicks, and by Dr. J. Madinaveitia to exert an antibacterial action against *Lactobacillus casei*, which was to some extent antagonized by riboflavin. Later, Dr. Davey found that the same substance had some trypanocidal activity *in vitro*, but not *in vivo* (against *Trypanosoma rhodesiense*).

After some delay the work was resumed and Table I gives a list of the *compounds* prepared. The first four differ only in the length of the polymethylene chain. One 7-chloro-compound (8021) and one 6-chloro-compound (5374) were prepared for comparison with their dichloro-analogues, 5115 and 5291, respectively. The 6 : 7-dichloro-3-methyl compound (8956) was made in order to discover the effect of blocking the possibility of lactam–lactim tautomerism in the *iso*alloxazine nucleus, and the methochloride (8955) to discover the effect of quaternizing the basic group; compound 8957 combines both these structural changes. Some difficulty was encountered in preparing the last compound in Table I, which contains the same side chain as mepacrine, and it has so far only been tested *in vitro.*

TABLE I.

iso*Alloxazines.*

Serial number.	Substituents in positions: 3.	6.	7.	9.	pK_a (±0·3) at 21°.
8776	—	Cl	Cl	$[CH_2]_2\cdot NHEt_2\}Cl$	7·7
5291	—	Cl	Cl	$[CH_2]_3\cdot NHEt_2\}Cl$	9·1
8778	—	Cl	Cl	$[CH_2]_4\cdot NHEt_2\}Cl$	9·7
8779	—	Cl	Cl	$[CH_2]_5NHEt_2\}Cl$	9·6
5115	—	Cl	Cl	$[CH_2]_3\cdot NH{<}C_5H_{10}\}Cl$	8·9
8021	—	—	Cl	$[CH_2]_3\cdot NH{<}C_5H_{10}\}Cl$	9·0
5374	—	Cl	—	$[CH_2]_3\cdot NHEt_2\}Cl$	9·8
8777	—	Cl	Cl	$[CH_2]_3\cdot NHBu_2\}Cl$	8·0
8955	—	Cl	Cl	$[CH_2]_3\cdot NMeEt_2\}Cl$	—
8956	Me	Cl	Cl	$[CH_2]_3\cdot NHEt_2\}Cl$	9·7
8957	Me	Cl	Cl	$[CH_2]_3\cdot NMeEt_2\}Cl$	—
9163	—	Cl	Cl	$CHMe\cdot[CH_2]_3\cdot NHEt_2\}X$ *	9·6

* X = Picrate anion.

The compounds were tested as antimalarial and trypanocidal agents in the laboratories of Imperial Chemical (Pharmaceuticals) Ltd. through the courtesy of the late Dr. F. H. S. Curd and Dr. D. G. Davey, but none of the compounds fulfilled the expectations aroused by the early tests on 5115; nor in later tests did the latter substance prove to be so active an antimalarial as had at first been thought. The 7-chloro-compound (8021) had slight activity against *T. congolense* in mice, and so had the quaternary salt 8955. The two 3-methyl compounds had slight to moderate activity against *T. rhodesiense* in mice, but none of the other compounds had any curative action against either parasite *in vivo.* The lack of curative activity in experimental malaria and trypanosomiasis may be partly due to the high toxicity of these compounds to chicks and mice, since positive effects were only observed with doses within the toxic range. The cause of this toxicity is unknown, but an action on the central nervous system is suspected.

The compounds were also tested in this laboratory, with the help of Dr. E. M. Lourie, against *T. rhodesiense in vitro*; they were trypanocidal in a dilution range of 1—2·5 million. Dr. Lourie tells us that with the same organism stilbamidine and pentamidine are trypanocidal in the ranges 1—4 and 6—8 million respectively (unpublished results), whereas undecanediamidine and tervalent arsenicals are active in dilutions of 1 in 100 million or more (King, Lourie, and Yorke, *Ann. Trop. Med. Parasit.*, 1938, **32**, 177).

On three flavoprotein enzymes, *viz.*, D-amino-acid oxidase, monoamine oxidase, and diamine oxidase, these compounds exerted only feeble inhibition; they had, however, the peculiar property of increasing the oxygen uptake of certain enzyme preparations, in particular those prepared from acetone-dried powders of liver and kidney. Dr. Madinaveitia had previously observed that, whereas 5115 inhibited the alcohol, citrate, and glycerophosphate dehydrogenases of yeast, yet it accelerated the action of yeast lactic acid dehydrogenase.

The pK_a values of all the tertiary bases were measured by the method of Albert and Goldacre (*J.*, 1943, 454); the results, included in Table I, are subject to an error of ±0·3 owing to the use of a mains-operated meter.

Professor Adrien Albert very kindly tested two of our compounds (5291 and its 3-methyl derivative 8956) for chelation effects by electrometric titration in the presence of cupric chloride. He reports that neither of these gave evidence of chelation; both behaved in the same way, although the former contains the unit $\cdot N{:}\dot{C}\cdot C(OH){:}N\cdot$, which might be expected to give rise to chelation, and the latter does not.

With the exception of the substance containing the 4-diethylamino-1-methylbutyl side chain, all the *iso*alloxazines were prepared by condensing suitably substituted *o*-phenylenediamines with alloxan monohydrate in methanol containing hydrogen chloride (Kuhling, *Ber.*, 1891, **24**, 2363); they were isolated as their crystalline *hydrochlorides*, which were usually hydrated, and occasionally as their *picrates.* The *o*-phenylenediamine derivatives were not usually isolated; they were obtained by catalytic reduction of the corresponding *o*-nitroaniline derivative in methanol and, after the removal of the catalyst, they were immediately condensed with alloxan. At first the *o*-nitroaniline derivatives were prepared by heating the appropriate ω-dialkylaminoalkylamine with 4 : 5-dichloro-1 : 2-dinitrobenzene, but as the preparation of the latter substance in quantity is exceedingly tedious (cf. Kuhn, Weygand, and Möller, *loc. cit.*), it was replaced by 2 : 4 : 5-trichloronitrobenzene, which is readily obtained by nitrating 1 : 3 : 4-trichlorobenzene; that it is the chloro-substituent *ortho* to the nitro-group which is replaced by the substituted alkylamine was proved by preparing three of the nitroaniline derivatives from both of these starting materials (see Table II). The *o*-nitroaniline derivatives were usually isolated as hydrochlorides or perchlorates, but reduction (with hydrogen and Raney nickel at atmospheric pressure) was best effected with the free bases in methanol; reduction of the hydrochlorides with hydrogen and palladium–charcoal was exceedingly slow.

The 6-chloro-compound (5374) was prepared by condensing 5-chloro-2-iodonitrobenzene with diethylaminopropylamine, reducing the *o*-nitroaniline derivative so formed, and condensing the product with alloxan. The 7-chloro-compound (8021) was similarly prepared from 2 : 4-dichloronitrobenzene and piperidinopropylamine.

Quaternary metho-salts of 9-dialkylaminoalkyl*iso*alloxazines could not be obtained by direct addition of methyl iodide to the free bases, or by condensing alloxan with the reduction products of *o*-nitro-*N*-dialkylaminoalkylaniline methiodides; intractable red products were formed by both methods. When, however, the *o*-nitro-*N*-dialkylaminoalkylaniline was converted into its methochloride (by the addition of methyl sulphite and subsequent hydrolysis of the metho-methylsulphite with hydrochloric acid), condensation with alloxan was satisfactorily effected after reduction of the nitro-group. The 3-methyl*iso*alloxazines were prepared by using methylalloxan in place of alloxan.

6 : 7-Dichloro-9-(4-diethylamino-1-methylbutyl)*iso*alloxazine hydrochloride could not be obtained by condensing the appropriate *o*-phenylenediamine derivative with alloxan in methanol containing hydrogen chloride; the only product isolated was 6 : 7-*dichloroalloxazine*. Other authors have found a similar difficulty in preparing *iso*alloxazines with the " mepacrine side chain " in position 9 (cf. Hall and Turner, *loc. cit.*; Kipnis, Weiner, and Spoerri, *loc. cit.*; McCombrey and Webster, *J.*, 1948, 1719), and Neeman (*loc. cit.*), who used boric acid in acetic acid as the condensing agent (Kuhn and Weygand, *Ber.*, 1935, **68**, 1282), was only able to isolate his products as reineckates. Condensation of alloxan with the reduction product of 4 : 5-*dichloro*-2-(4-*diethylamino*-1-*methylbutylamino*)*nitrobenzene* certainly occurs in acetic acid solution in the presence of boric acid, since we were able to isolate the *iso*alloxazine as its *picrate*, but we were unable to isolate the hydrochloride in an analytically pure state.

EXPERIMENTAL.

(All analyses are by Drs. Weiler and Strauss. All m. p.s are uncorrected.)

Dialkylaminoalkylamines.—We are indebted to Messrs. Imperial Chemical Industries Ltd. for generous supplies of diethylamino-ethylamine and -propylamine, dibutylaminopropylamine, and 4-diethylamino-1-methylbutylamine. Diethylamino- and piperidino-propylamines were prepared by the method of Whitmore *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 725), the intermediate nitriles being reduced by sodium and ethanol. Diethylaminobutylamine was prepared from γ-chlorobutyronitrile (Utermohlen and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 156; Strukov, *Chem. Abs.*, 1934, **28**, 3714), and the homologous amylamine from phthalo-5-bromoamylimide (Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396).

2-*Nitro*-N-*dialkylaminoalkylanilines.*—The 4 : 5-dichloro-2-nitrodialkylaminoalkylanilines were all prepared by boiling a solution of the dialkylaminoalkylamine and 2 : 4 : 5-trichloronitrobenzene (10% excess) in toluene or xylene for 5—12 hours; yields of 40—50% were obtained. Three of them (see Table II) were also prepared in a similar way from the alkylamine and 4 : 5-dichloro-1 : 2-dinitrobenzene. 5-*Chloro*-2-*nitro*-N-3′-*piperidinopropylaniline hydrochloride* was obtained similarly from piperidinopropylamine and 2 : 4-dichloronitrobenzene. The reaction mixtures were cooled and shaken with dilute hydrochloric acid; if the solid hydrochloride separated, it was collected and crystallized from water or alcohol; otherwise, the free base was liberated to ether and converted into the perchlorate. Only one base was obtained crystalline, *viz.*, 4 : 5-*dichloro*-2-*nitro*-N-2′-*diethylaminoethylaniline.*

4-*Chloro*-2-*nitro*-N-3′-*diethylaminopropylaniline hydriodide* was obtained by heating together diethylaminopropylamine and 5-chloro-2-iodonitrobenzene (Korner, *Gazzetta*, 1875, **4**, 381) without a solvent at 100° until a test drop gave a clear solution in dilute acid (4 hours). The product was diluted with water and acidified with hydriodic acid, the salt then crystallizing; it was recrystallized by the addition of ether to its solution in hot ethanol.

Table II gives a list of the compounds prepared, their m. p.s, and analytical results. The salts tend to crystallize in orange or yellow hydrated forms; the anhydrous salts are red, but become yellow in a damp atmosphere. The hydrochlorides are soluble in water and alcohol, but only sparingly so in acetone; the perchlorates are less soluble in water and alcohol. The *methochloride* of 4 : 5-dichloro-2-nitro-*N*-3′-diethylaminopropylaniline was obtained by heating the free base in methanol with methyl sulphite (1 mol.; excess must be avoided); after 1 hour, excess of hydrochloric acid was added, and heating continued for 4 hours; the solution was then evaporated and the residue taken up in ethanol and again evaporated; it was finally crystallized from ethanol. Both the methochloride (orange) and the *methiodide* (yellow) were hydrated; they lost water, becoming red, a few degrees above 100°.

2 : 4 : 5-Trichloronitrobenzene was prepared by adding 1 : 2 : 4-trichlorobenzene (25 c.c.) gradually to nitric acid (*d* 1·5; 120 c.c.) cooled in ice–salt; the solution was poured on ice, and the mixture left at 0°

TABLE II.

2-Nitro-N-*dialkylaminoalkylanilines.*

Method.	Substituents. 4.	5.	*N.*	Salt.	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
a	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	—	102° *	$C_{12}H_{17}O_2N_3Cl_2$	47·1	5·4	—	47·1	5·6	—
a, b	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	214	$C_{13}H_{20}O_2N_3Cl_3$ †	—	—	11·5	—	—	11·8
				MeI	215	$C_{14}H_{22}O_2N_3Cl_2I,H_2O$	35·0	5·0	—	35·0	5·0	—
				MeCl	216	$C_{14}H_{22}O_2N_3Cl_3,H_2O$	43·2	5·7	—	43·3	6·2	—
a	Cl	Cl	$[CH_2]_4{\cdot}NEt_2$	HCl	133 ‡	$C_{14}H_{22}O_2N_3Cl_3,\frac{1}{2}H_2O$	44·2	6·1	10·8	44·3	6·1	11·1
				$HClO_4$	143 ‡	$C_{14}H_{22}O_6N_3Cl_3$	—	—	9·8	—	—	9·7
a	Cl	Cl	$[CH_2]_5{\cdot}NEt_2$	$HClO_4$	133 ‡	$C_{15}H_{24}O_6N_3Cl_3$	39·7	4·9	—	40·2	5·4	—
a, b	Cl	Cl	$[CH_2]_3{\cdot}NC_5H_{10}$	HCl	215	$C_{14}H_{20}O_2N_3Cl_3$	—	—	11·2	—	—	11·4
a	Cl	Cl	$[CH_2]_3{\cdot}NBu_2$	$HClO_4$	140 ‡	$C_{17}H_{28}O_6N_3Cl_3$	42·9	5·8	—	42·8	5·9	—
a, b	Cl	Cl	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	$HClO_4$	109	$C_{15}H_{24}O_6N_3Cl_3$	—	—	9·5	—	—	9·4
c	Cl	H	$[CH_2]_3{\cdot}NEt_2$	HI	157	$C_{13}H_{21}O_2N_3ClI$	37·9	5·0	—	37·7	5·1	—
d	H	Cl	$[CH_2]_3{\cdot}NC_5H_{10}$	HCl §	210	$C_{14}H_{21}O_2N_3Cl_2$	49·3	6·0	—	49·0	6·4	—

(*a*) Prepared from 2 : 4 : 5-trichlorobenzene.

(*b*) Prepared from 4 : 5-dichloro-1 : 2-dinitrobenzene.

(*c*) Prepared from 5-chloro-2-iodonitrobenzene.

(*d*) Prepared from 2 : 4-dichloronitrobenzene.

* Free base, crystallized from ether.

† Found : Cl, 29·8. $C_{13}H_{20}O_2N_3Cl_3$ requires Cl, 29·9%.

‡ Melting with decomposition.

§ Crystallized with $\frac{1}{2}H_2O$ (Found : H_2O, 2·7. $C_{14}H_{20}O_2N_3Cl,HCl,\frac{1}{2}H_2O$ requires H_2O, 2·6%) but the analysis in the Table is for the anhydrous salt.

TABLE III.

*9-Dialkylaminoalkyl*iso*alloxazines.*

Substituents : 3.	6.	7.	9.	Salt.	Cryst. from	M. p.*	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
—	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	HCl	H_2O–MeOH	286°	$C_{16}H_{18}O_2N_5Cl_3,\frac{1}{2}H_2O$	46·0	4·4	16·6	45·9	4·1	16·7
CH_3	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	HCl	H_2O–EtOH	244	$C_{17}H_{20}O_2N_5Cl_3,H_2O$	45·8	4·9	15·6	45·3	4·9	15·6
—	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	H_2O–EtOH	244	$C_{17}H_{20}O_2N_5Cl_3,H_2O$	45·5	4·9	15·6	45·3	4·9	15·6
				HCl †	MeOH–Et_2O	244	$C_{17}H_{20}O_2N_5Cl_3,1\frac{1}{2}H_2O$	43·9	5·0	15·0	44·4	4·0	15·2
				MeCl	H_2O–EtOH	276	$C_{18}H_{22}O_2N_5Cl_3,2H_2O$	44·1	5·0	15·0	44·8	5·4	14·5
				Me p.‡	H_2O–EtOH	130	$C_{24}H_{24}O_9N_8Cl_2,H_2O$	43·8	3·7	17·1	43·8	3·9	17·0
CH_3	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	EtOH	240	$C_{18}H_{22}O_2N_5Cl_3,1\frac{1}{2}H_2O$	45·3	4·8	15·3	45·6	5·3	14·8
				p. ¶	H_2O–EtOH	215	$C_{24}H_{24}O_9N_8Cl_2$	44·6	3·1	17·7	45·1	3·8	17·5
				MeCl	H_2O–EtOH	248	$C_{19}H_{24}O_2N_5Cl_3,\frac{1}{2}H_2O$	48·2	5·0	15·3	48·6	5·3	14·9
				Me p.	EtOH	204	$C_{25}H_{26}O_9N_8Cl_2$	45·5	3·8	17·3	46·0	4·0	17·2
—	Cl	Cl	$[CH_2]_4{\cdot}NEt_2$	HCl	H_2O–EtOH	259	$C_{18}H_{22}O_2N_5Cl_3,1\frac{1}{2}H_2O$	45·8	5·1	15·1	45·7	5·3	14·8
				p.	H_2O–EtOH	236	$C_{24}H_{24}O_9H_8Cl_2$	45·3	4·0	17·1	45·1	3·8	17·5
—	Cl	Cl	$[CH_2]_5{\cdot}NEt_2$	HCl	AcOH	252	$C_{19}H_{24}O_2N_5Cl_3,H_2O$	47·5	5·0	13·9	47·7	5·4	14·6
				p.	H_2O–EtOH	247	$C_{25}H_{26}O_9N_8Cl_2$	46·3	4·0	17·3	46·0	4·0	17·2
—	Cl	Cl	$[CH_2]_3{\cdot}N{<}C_5H_{10}$	HCl §	AcOH–Et_2O	271	$C_{18}H_{20}O_2N_5Cl_3,H_2O$	46·9	5·0	15·1	46·7	4·8	15·1
—	Cl	Cl	$[CH_2]_3{\cdot}NBu_2$	HCl	EtOH	246	$C_{21}H_{28}O_2N_5Cl_3,\frac{1}{2}H_2O$	50·5	6·1	13·8	50·5	5·8	14·1
				p.	EtOH–$COMe_2$	223	$C_{27}H_{30}O_9N_8Cl_2$	47·5	4·8	16·4	47·6	4·4	16·4
—	Cl	Cl	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	p.	EtOH–$COMe_2$	209	$C_{25}H_{26}O_9N_8Cl_2$	45·6	4·6	17·3	46·0	4·0	17·2
—	Cl	—	$[CH_2]_3{\cdot}NEt_2$	HCl	AcOH–$COMe_2$	282	$C_{17}H_{21}O_2N_5Cl_2$	50·9	4·9	17·7	51·2	5·3	17·6
—	—	Cl	$[CH_2]_3{\cdot}N{<}C_5H_{10}$	HCl	AcOH	275	$C_{18}H_{21}O_2N_5Cl_2$	52·4	5·3	16·6	52·6	5·1	17·1

* All salts melt with decomposition.

† Found : H_2O, 5·8. $C_{17}H_{20}O_2N_5Cl_3,1\frac{1}{2}H_2O$ requires H_2O, 5·9%.

‡ Found : H_2O, 2·3. $C_{24}H_{24}O_9N_8Cl_2,H_2O$ requires H_2O, 2·7%.

§ Found : H_2O, 3·9. $C_{18}H_{20}O_2N_5Cl_3,H_2O$ requires H_2O, 3·9%.

¶ p. = picrate.

overnight. The solid was collected, sucked as dry as possible from oily products, and crystallized twice from methanol; m. p. 57°; yield 20 g., 50—60% (Jungfleisch, *Ann. Chim. Phys.*, 1868, **15**, 273).

The iso*Alloxazine Condensation.*—The 2-nitro-alkylaminoalkylanilines were liberated from their salts to ether, the ethereal extracts dried (Na_2SO_4) and evaporated, and the free bases dissolved in methanol and reduced with hydrogen and Raney nickel at atmospheric pressure. After removal of the catalyst, hydrogen chloride was bubbled into the solution, and alloxan monohydrate (1 mol.) added; the hydrogen chloride stream was continued until the blue colour, which formed round the alloxan crystals, had disappeared and the solution was strongly acid to Congo-red. Sufficient heat was usually generated by this procedure to effect dissolution of the alloxan, but occasionally additional heating was necessary. The deep-brown solution was set aside for at least 12 hours. The *iso*alloxazine hydrochloride sometimes crystallized from the reaction mixture; if not, it was precipitated as a dark brown oil or gum by addition of ether; the mother-liquor from any crystalline material was also treated in this way. The gummy salt often crystallized when stirred with ethanol, but sometimes further washing with ether or acetone was necessary before crystallization could be induced. The *hydrochlorides* were all readily soluble in water with a brilliant green fluorescence, but sparingly so in ethanol. They were usually crystallized from aqueous ethanol and, with the exception of the 6-chloro- and the 7-chloro-compound, they were all hydrated; the two *methochlorides* behaved similarly. The *picrates*, with one exception, crystallized anhydrous and provided a convenient way of characterizing these *iso*alloxazine derivatives. Table III gives a list of the compounds prepared, with m. p.s and analytical results. Usually the yield of recrystallized product was about 30—40%.

4 : 7-Dichloro-9-(4-diethylamino-1-methylbutyl)*iso*alloxazine was prepared in a crude state from the appropriate *o*-nitroaniline derivative by the method of Kipnis, Weiner, and Spoerri (*loc. cit.*). Several attempts were made to prepare a hydrochloride from the crude base, but without success. The *picrate*, however, crystallized from aqueous alcohol–acetone (Table III). When methanolic hydrogen chloride was used as the condensing medium, an insoluble white product separated which appeared to be 6 : 7-*dichloroalloxazine*; it was insoluble in all the usual solvents, but dissolved in aqueous alkali and was reprecipitated by carbon dioxide; it did not melt below 300° (Found : N, 19·8. $C_{10}H_4O_2N_4Cl_2$ requires N, 19·8%).

The methylalloxan used in the preparation of the 3-methyl*iso*alloxazines was prepared from theobromine by the method of Biltz (*Ber.*, 1912, **45**, 3659). In our experience it is essential to use " AnalaR " stannous chloride in the reduction stage and to keep the reaction solution at −15° for 24 hours in order to induce dimethylalloxantin to crystallize.

We are indebted to the Medical Research Council for a research grant to one of us and a training grant to the other.

DEPARTMENT OF PHARMACOLOGY, OXFORD. [*Received, December 13th*, 1949.]

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145. *Fucoidin. Part I. The Isolation and Purification of Fucoidin from Brown Seaweeds.*

By E. G. V. PERCIVAL and A. G. ROSS.

The isolation of the polysaccharide sulphate, fucoidin, from various species of *Phæophyceæ* is described and the results of quantitative analyses are reported.

FUCOIDIN, the principal polysaccharide sulphate ester of the *Phæophyceæ*, differs from that of the *Rhodophyceæ* in that the main carbohydrate skeleton is founded on fucose instead of on galactose.

Fucoidin which occurs together with mannitol, alginic acid and laminarin, was first described and named by Kylin (*Z. physiol. Chem.*, 1913, **83**, 171; 1915, **94**, 357) who isolated the substance from various species of *Laminaria* and *Fucus* by extraction with dilute acetic acid and subsequent purification. After hydrolysis Kylin isolated phenyl-L-fucosazone and claimed that pentoses were present also in the hydrolysate.

Bird and Haas (*Biochem. J.*, 1931, **25**, 403) obtained fucoidin by soaking fresh fronds of *Laminaria digitata* in water and precipitating a crude sulphate from the viscous extract with ethanol. After suitable treatment a product containing 30·9% of ash (chiefly calcium sulphate) and 30·3% of sulphate was obtained.. Since the total sulphate content was approximately double that found in the ash, fucoidin was designated a carbohydrate ethereal sulphate. Bird and Haas (*loc. cit.*) reported the presence of uronic acid (7·3%) in their preparation.

Lunde, Heen, and Öy (*Z. physiol. Chem.*, 1937, **247**, 189) allowed the droplets exuding from freshly-gathered *Laminaria digitata* to fall into ethanol, and, after its purification from boiling ethanol, obtained a specimen with an ash content of 26—30% of which the sulphate content was approximately half the total estimated in the polysaccharide. In this specimen the principal inorganic ion was sodium. Estimations by distillation with hydrochloric acid gave 33—37% of methylpentose, and since this failed to account for more than 80% of the carbohydrate constituents a formula $(R{\cdot}R'{\cdot}O{\cdot}SO_2{\cdot}OM)_n$ was proposed where R is fucose (as $C_6H_{10}O_4$), R′ is unknown, and M may be Na, K, $Ca_{0{\cdot}5}$ or $Mg_{0{\cdot}5}$.

Another water-soluble polysaccharide closely related to, if not identical with, fucoidin was first isolated from the giant kelp *Macrocystis pyrifera* (Hoagland and Lieb, *J. Biol. Chem.*, 1915, **23**, 287) and shown to contain L-fucose and a high proportion of calcium and sulphate. Further studies by Nelson and Cretcher (*ibid.*, 1931, **94**, 147) revealed that the sulphate existed in the form of ester groupings, and that the only sugar identified after hydrolysis was L-fucose, although contamination with alginates was suspected on the ground of a uronic acid content of 2·6%.

In an attempt to reconcile some of the conflicting views on the nature of fucoidin, specimens have been prepared from *Fucus vesiculosus*, *Fucus spiralis*, *Laminaria cloustoni*, and *Himanthalia lorea*. The method adopted was by extraction with hot water, removal of alginates and proteins with lead acetate, and addition of barium hydroxide. The resulting lead hydroxide–fucoidin complex was then decomposed with dilute sulphuric acid, and the polysaccharide isolated after prolonged dialysis, although several treatments with "Filter Cel" and precipitation from ethanol were necessary before anything approaching a pure product was obtained. The presence of a sulphate ester was confirmed in the usual way for all our specimens; in contrast to the findings of Lunde *et al.* (*loc. cit.*) the main inorganic ion was found to be calcium, a typical ash analysis giving Ca 25·0, Mg 1·9, Na 1·1, K 0·8, and SO_4 73·2%. The earlier specimens examined contained glucose, presumably owing to the incomplete removal of laminarin. In the Table the results for a number of specimens of fucoidin are set out. Fucose was estimated by the method of Cameron, Ross, and Percival (*J. Soc. Chem. Ind.*, 1948, **67**, 161) although it was found later that slightly higher values were obtained by chromatographic analysis.

Source.	Fucose, %.	SO_4, %.	Metals, %.	Ca, %.	$[\alpha]^{15}_{D}$.
F. vesiculosus	37·4	31·7	—	—	−119°
F. spiralis	35·8	32·7	6·4	5·8	−118
L. cloustoni	36·5	33·5	7·1	6·1	−114
F. vesiculosus	41·2	33·6	6·5	—	—
Himanthalia lorea	43·9	32·4	6·9	—	−140

Since a calcium fucosan sulphate would give 66·9% of fucose on hydrolysis it appeared that the view held by Lunde had some justification. Nevertheless a prolonged search by various methods, including periodate oxidation of hydrolysis products and chromatographic analysis, failed to reveal the presence of more than small quantities of other sugars. The discrepancy was accounted for when it was realised that despite drying at 40°/0·1 mm. for 18 hours, the polysaccharide stubbornly retained water (9·4%) and ethanol (6%) as revealed by micro-Zerewitinow determinations and by the use of the method of Newman (*J. Pharmacol.*, 1936, **56**, 278) for the determination of ethanol.

This result recalls the observations of Berner (*Ber.*, 1931, **64**, 842) on the difficulty of removing adsorbed ethanol from inulin, and those of Jansen, MacDonnell, and Ward (*Arch. Biochem.*, 1949, **21**, 149) on the retention of ethanol by polygalacturonic esters. In the present instance the attraction for water is probably enhanced by the presence of the sulphate residues.

After making due allowances for the adsorbed solvents, and by chromatographic estimations of the reducing sugars present, the following result was obtained for the most highly purified specimen of *Himanthalea lorea* fucoidin: SO_4, 38·3; metals, 8·2; uronic acid, 3·3; fucose on hydrolysis, 56·7; galactose, 4·1; xylose, 1·5%. A calcium fucosan monosulphate $(C_6H_9O_3,SO_4Ca_{0{\cdot}5})_n$ would give: SO_4, 39·2; Ca, 8·2; fucose 66·9%.

The simplest interpretation of these results is that the principal constituent of the fucoidin examined is a fucosan monosulphate and that the other constituents arise from adventitious impurities.

EXPERIMENTAL,

Isolation of Crude Fucoidin from Seaweeds.—Samples of crude fucoidin were prepared from *Fucus vesiculosus*, *F. spiralis*, *Laminaria cloustoni*, and *Himanthalea lorea* as follows: For the first specimens, dried ground seaweed (1 kg.) was extracted with hot water (3 l.) for 24 hours at the temperature of a boiling water-bath and the residue removed by filtration through muslin. The extract was treated with lead acetate solution until precipitation of alginates and proteins was complete. After filtration the solution was made just alkaline to phenolphthalein with barium hydroxide, yielding a lead hydroxide–fucoidin complex which was removed and decomposed with dilute sulphuric acid (300 c.c. of 4N-acid in 1 l. of water) by shaking overnight, followed by dialysis for a week in a Cellophane bag to remove the acid, filtration, evaporation (40°/15 mm.) to small bulk, and precipitation in alcohol. The resulting solid, which was washed with alcohol and ether and dried over phosphoric oxide in a vacuum, was buff-coloured and a representative analysis was: fucose (by the method of Cameron, Ross, and Percival, *loc. cit.*), 29·6; SO_4, 27·3%. Yields: *F. vesiculosus*, 23 g.; *F. spiralis*, 18 g.; *L. cloustoni*, 8 g.

Since the determination of fucose required the preliminary hydrolysis of the polysaccharide, the rate of hydrolysis of the sample from *F. vesiculosus* was followed polarimetrically; hydrolysis was complete in 3 hours in 0·5N-sulphuric acid, the rotation rising from $[\alpha]_D^{18}$ −119° to −24°.

Further Purification of Fucoidin.—Dissolution in water, followed by evaporation and reprecipitation in alcohol, did not increase the fucose content but, if the solution in water was set aside overnight with 2% Johns-Manville " Filter Cel " and then filtered and the product was isolated as before, the fucose released on hydrolysis of the sample noted before rose to 35·4% and a second treatment increased this figure to 37·4%, the total sulphate rising to 31·7%. The samples from other species of seaweed gave similar figures when treated in the same way although these operations involved serious loss of material. Sulphate, metals, and $[\alpha]_D$ were also determined (see foregoing Table).

The sample of crude polysaccharide prepared from *Himanthalea lorea* was extracted from freshly gathered, minced seaweed (50 kg.) as before except that, after decomposition of the lead hydroxide precipitate with acid, the mixture was filtered through " Filter Cel " which removed much colouring matter. The fucoidin (190 g.) was separated after concentration and precipitation in alcohol. This product (20 g.) was redissolved in water and treated twice with charcoal (1%; Merck) and " Filter Cel " (2%) at 90° for ½ hour, yielding after filtration and isolation a pure white product (12 g.) containing fucose 43·9%, SO_4 32·4%, ash 22·6%, and metals 6·9%. This sample, which was used for the later analyses unless otherwise stated, was the most highly purified specimen obtainable by this method, two additional treatments giving a product with the same analytical figures and $[\alpha]_D^{15}$ −140° (*c*, 1·0 in water).

Investigation of Other Components of Crude Fucoidin.—Before the fucoidin was obtained from *H. lorea*, some investigations were made into the undetermined portion of the polysaccharide from *F. vesiculosus*.

Estimation of pentose (Marshall and Norris, *Biochem. J.*, 1937, **31**, 1289, 1939) and uronic acid (MacCready, Swenson, and Maclay, *Ind. Eng. Chem. Anal.*, 1946, **18**, 290) gave figures of 3·4% and 6·6% respectively, but no free sugars or methoxyl groups could be detected. Hypoiodite oxidation after hydrolysis, on the other hand, indicated about 20% of sugars as hexose after allowance for fucose, by addition of excess of alkaline hypoiodite and titration of the excess with thiosulphate after storage for 1 hour and acidification. Oxidation experiments using periodic acid were also carried out after preliminary investigations into the oxidation of glucose and rhamnose. On treatment with periodic acid pentoses and hexoses yield 1 molecule of formaldehyde along with formic acid (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476), the formaldehyde being estimated as the dimedon complex (Vorländer, *Z. Analyt. Chem.*, 1929, **77**, 241). In the present case glucose was found to give 0·96 mol. of formaldehyde when treated in admixture with rhamnose, provided that the acetaldehyde formed from the methylpentose was removed by aeration before precipitation with dimedon. The formic acid liberated was also determined by titration after destruction of the excess of periodate with ethylene glycol, glucose giving 4·90 mols. and rhamnose 3·99 mols. of formic acid. When applied to fucoidin, the production of formaldehyde was equivalent to 19·1% of hexose, and that of formic acid after allowance for fucose to 14·8% of hexose.

A sample of fucoidin was hydrolysed and the fucose mainly removed as the phenylmethylhydrazone, the remaining material, after treatment with benzaldehyde (Lüdtke, *Biochem. Z.*, 1929, **212**, 419), being finally obtained as a glass. A small amount of alcohol-insoluble material was shown to be mainly uronic acid whilst the soluble portion contained fucose 5·4% and hexose (by periodate oxidation) 51·9%. This gave glucosazone (m. p 186°) which yielded phenyl-D-glucosotriazole (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1945, **67**, 939) (m. p. 196—197°, mixed m. p. 193—194°, $[\alpha]_D^{18}$ −80° in pyridine). These results indicate the presence of glucose since it was found impossible to obtain mannose phenylhydrazone under conditions in which a control mannose solution reacted readily. Estimation of the glucose by the Somogyi micro-copper method (*J. Biol. Chem.*, 1945, **160**, 61) before and after incubation with yeast at 37° (Harding and Selby, *Biochem. J.*, 1931, **25**, 1815) indicated the presence of 15·8% of glucose in the glass along with a similar amount of another reducing sugar, not absorbed by yeast, which was not identified.

Properties of Fucoidin as a Free Acid.—Freshly prepared fucoidin solution (0·2%) had a pH value of 6·1 which fell to 4·0 on storage for 1 week owing to autohydrolysis. Fucoidin (0·35 g.) was dissolved in water (150 c.c.), and the solution titrated electrometrically with sodium hydroxide (0·01N.) with a platinum–quinhydrone–N-calomel cell. After titration to a pH of 7·26, the calculated amount of oxalic acid necessary to precipitate exactly the calcium present was added and the titration of the free acid continued using sodium hydroxide (0·1N.). The results in the following table indicate the presence of a strong acid.

C.c. of NaOH (0·1045N.) added ...	—	1·0	3·0	5·0	6·0	7·0	9·0	9·5	9·6	9·7
pH	3·72	3·74	3·91	4·45	4·63	4·96	5·79	6·84	7·16	7·26

Further Analyses of the Purest Fucoidin from H. lorea.—All analyses were carried out on samples dried at 40°/0·1 mm. for 16 hours. This sample contained fucose 43·9% and SO_4 32·4%. Quantitative paper chromatographic analysis (Flood, Hirst, and Jones, *J.*, 1948, 1679) on this material, after hydrolysis, gave fucose 48·4%, which is slightly higher than that obtained by the volumetric estimation. Fucoidin (1·247 g.) was hydrolysed with sulphuric acid (100 c.c.; N.) and neutralised, and the free sugars were obtained as a glass, all the operations being carried out as far as possible quantitatively. The glassy product (0·755 g. or 60·5%) had $[\alpha]_D^{15}$ −54·8 (*c*, 1·26 in water), fucose 75·0%, sulphate as calcium sulphate 7·8%, and sulphated ash 7·2%. A quantitative paper chromatogram on the glass gave fucose 79·1% and galactose 7·2%, representing 48·0% and 4·4% respectively calculated on the polysaccharide. Development of a chromatogram with aniline oxalate solution confirmed the presence of hexose (brown spot) and also indicated a small quantity of a pentose (pink spot) corresponding to xylose. A second quantitative determination using more material was carried out and gave galactose amounting to 5·8% and xylose 2·2% of the glass.

The analytical figures to date on the polysaccharide were fucose 48·0%, galactose 3·5%, xylose 1·3%, uronic acid 2·8%, sulphate 32·4%, and metals 6·9%. Calculation of these figures to anhydrosugars, etc., as in the polysaccharide showed that about 15% remained to be accounted for.

Alcohol determinations were carried out by the method of Newman (*J. Pharmacol.*, 1936, **56**, 278) on samples dried for 18 hours at 40°/0·1 mm. The alcohol is removed from the sample by evacuation after dissolution in water and addition of anhydrous sodium sulphate, and is absorbed in acid dichromate solution; the excess of dichromate is then titrated with sodium thiosulphate in the presence of potassium iodide. Found: adsorbed alcohol 6·0% (average of three determinations). Adsorbed water was also investigated and determined by means of the Zerewitinow reaction (*Ber.*, 1907, **40**, 2033) modified to the micro-determination of active hydrogen (Flaschenträger, *Z. physiol. Chem.*, 1925, **146**, 219; Pregl–Grant, "Quantitative Organic Micro-analysis," 4th Edn., 1945), allowance being made for the active hydrogen in the ethanol in the polysaccharide. It was found that methane was produced equivalent to 9·5% of water in the polysaccharide. The possibility of other reactions taking place was negatived by a similar determination on starch with a known moisture content of 12·1% (Found: water 12·7%). By weighing a supposedly dry sample of fucoidin at intervals after storage in an atmosphere of 60% relative humidity, it was found that after 1 day the moisture content increased by 17% and, after 6 days, by 26%, showing that intensive drying before analysis is necessary and confirming the possibility of fucoidin's high power of retaining water after being dried by the normal methods.

The addition of water and alcohol to the previous analytical figures brings the total percentage accounted for to 99·3%.

Thanks are expressed to the Scottish Seaweed Research Association for permission to publish this work.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, December* 13*th*, 1949.]

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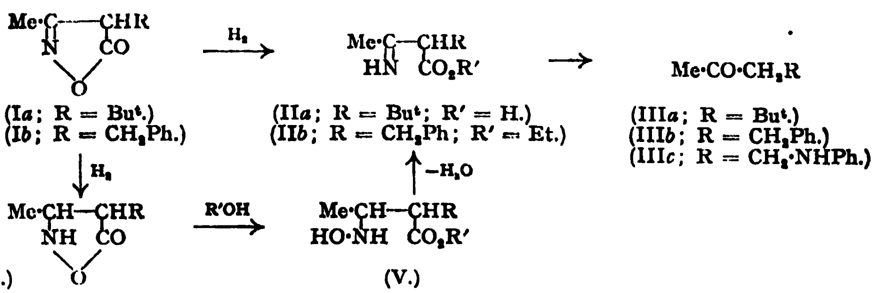
146. *The Hydrogenation of Some* iso*Oxazolones.*

By G. SHAW.

Hydrogenation of 4-benzylidene-3-methyl- and 3-methyl-4-anilinomethylene-*iso*oxazolones using a palladium catalyst affords the 4-benzyl- and 4-anilinomethyl-*iso*oxazolones. When a platinum catalyst is used in moist solvents, disruption of the *iso*oxazolone nucleus occurs and linear ketones are obtained; in anhydrous ethanol hydrogenation of the 4-benzylidene- and 4-benzyl-*iso*oxazolones affords ethyl α-benzylacetoacetate, suggesting the formation of a reactive anhydride-like substance, possibly an *iso*oxazolidone (IV). Hydrogenation of propiophenone oxime acetate affords the corresponding acylketimine. Oxidation of propiophenone acetylimine with potassium permanganate in acetone, in an attempt to reverse the last-mentioned reaction, gives *N*-acetylbenzamide.

IT has been shown recently (Panizzi, *Gazzetta*, 1946, **76**, 44) that hydrogenation of 3-methyl-4-*tert.*-butyl*iso*oxazol-5-one (I*a*), using a large excess of platinum as catalyst and acetic acid as solvent, affords *tert.*-butylacetone (III*a*); Panizzi points out the unexpected lability of oxygen in the *iso*oxazolone nucleus and suggests that ketone formation is preceded by formation of β-imino-α-*tert.*-butylbutyric acid (II*a*). Evidence is now presented which suggests that hydrogenation of the *iso*oxazolone system produces a reactive anhydride-like substance, possibly the *iso*oxazolidone (IV) which may yield (II) *via* the hydroxylamine derivative (V).



(I*a*; R = Buᵗ.)
(I*b*; R = CH₂Ph.)

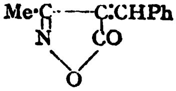
(II*a*; R = Buᵗ; R' = H.)
(II*b*; R = CH₂Ph; R' = Et.)

(III*a*; R = Buᵗ.)
(III*b*; R = CH₂Ph.)
(III*c*; R = CH₂·NHPh.)

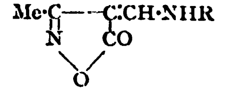
(IV.)

(V.)

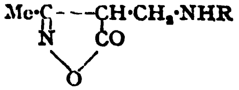
Hydrogenation of 4-benzylidene-3-methyl*iso*oxazol-5-one (VI) over 5% palladium–charcoal in ethanol or ethyl acetate at room temperature resulted in the absorption of only 1 mole of hydrogen and formation of 4-benzyl-3-methyl*iso*oxazol-5-one (I*b*). Hydrogenation of the basic arylaminomethylene*iso*oxazolones (VII*a*—*c*) under the same conditions afforded quantitative yields of the corresponding *arylaminomethyl*iso*oxazolones* (VIII*a*—*c*) which readily formed *picrates*.



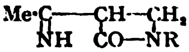
(VI.)



(VII*a*; R = Ph.)
(VII*b*; R = *o*-tolyl.)
(VII*c*; R = *p*-tolyl.)



(VIII*a*; R = Ph.)
(VIII*b*; R = *o*-tolyl.)
(VIII*c*; R = *p*-tolyl.)



(IX.)

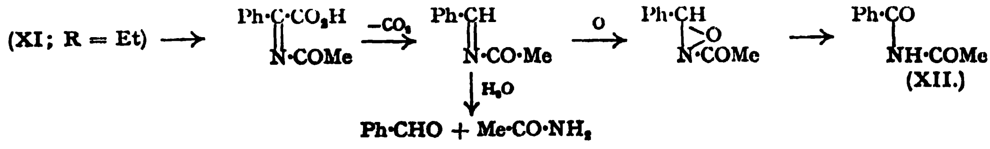
It soon appeared that Adams's platinum catalyst was required for the disruption of the *iso*oxazolone nucleus: when thus reduced in ethanol or ethyl acetate, (VI) absorbed 2 moles of hydrogen affording ammonia and an oil consisting largely of 4-phenylbutan-2-one (III*b*). Under the same conditions 4-benzyl-3-methyl*iso*oxazol-5-one (I*b*) absorbed 1 mole of hydrogen and gave the same products. In these experiments no special precautions were taken to exclude moisture. When (I*b*) was reduced with hydrogen–platinum in absolute ethanol under anhydrous conditions 1 mole of hydrogen was absorbed but no ammonia was formed, and from the reaction mixture was isolated ethyl α-benzylacetoacetate and a base which was rapidly hydrolysed to the keto-ester and was probably its imine (II*b*). The identity of the keto-ester was confirmed by conversion by warm concentrated sulphuric acid into 1-methylindene-2-carboxylic acid (von Pechmann, *Ber.*, 1883, **16**, 516; Roser, *Annalen*, 1888, **247**, 157). The keto-ester was also obtained by reduction of (VI) under anhydrous conditions in absolute ethanol, but neither (VI) nor (I*b*) showed evidence of reaction with ethanol at room temperature Hydrogenation of 3-methyl-4-anilinomethylene*iso*oxazol-5-one (VII*a*) in moist solvents afforded ammonia and 4-anilinobutan-2-one (III*c*), but in anhydrous solvents a viscous liquid was obtained which could not be satisfactorily identified; work in this direction is being pursued to ascertain the possibility of formation of an azetidinone or β-lactam (IX) which might conceivably arise by rearrangement of the hypothetical *iso*oxazolidone (IV; R = CH_2·NHPh).

The isolation of ethyl α-benzylacetoacetate by reduction of (I*b*) and (VI) in ethanol implies the intermediate formation of an anhydride-like substance capable of combining with the solvent and this substance is postulated provisionally as the *iso*oxazolidone (IV). Attempts to isolate such a compound by carrying out the reduction in anhydrous ethyl acetate were unsuccessful, a viscous oil being obtained from which benzylacetone alone could be isolated.

The system –C:N·O·CO– exists in the acyloximes (X) and hydrogenation of these substances was next attempted in the hope that the stable acylketimines (XI) might be obtained. Moureu

(X.) Ph·CR:N·O·COMe Ph·CR:N·COMe (XI.)

and Mignonac (*Compt. rend.*, 1913, **156**, 1805; 1920, **170**, 1354) showed that reduction of oximes with hydrogen–platinum afforded the ketimines and prepared a number of acylketimines by acylation of these substances and also by an independent method. In presence of platinum in ethanol propiophenone oxime acetate (X; R = Et) absorbed 1 mole of hydrogen during 4 hours, to afford propiophenone *N*-acetylimine (XI; R = Et), identical with a sample prepared from phenylmagnesium bromide, propionitrile, and acetyl chloride (Moureu and Mignonac, *loc. cit.*). Hydrogenation of acetophenone oxime acetate (X; R = Me) under the same conditions afforded an oil which was presumably the ketimine (XI; R = Me) since it gave acetophenone, ammonia, and acetic acid when hydrolysed. In an attempt to reverse the latter reaction, propiophenone *N*-acetylimine (XI; R = Et) was treated with potassium permanganate in acetone, but, instead of the expected oxime acetate, *N*-acetylbenzamide (XII) was obtained in good yield, together with a small amount of benzaldehyde. This suggests that the oxidation may proceed according to the scheme:



(XII.)

EXPERIMENTAL.

Hydrogenations were carried out at room temperature and atmospheric pressure; the recorded volumes of hydrogen refer to N.T.P.

*Hydrogenation of 4-Benzylidene-3-methyl*iso*oxazol-5-one* (VI).—The *iso*oxazolone (1 g.; Dains and

Griffin, *J. Amer. Chem. Soc.*, 1913, **35**, 959) in 90—95% ethanol (30 ml.) was reduced with hydrogen and 5% palladium–charcoal (0·1 g.), hydrogen (131 ml. Calc. for 1 mol., 120 ml.) being absorbed during 1 hour. Evaporation of the filtered solution *in vacuo* gave an oil which partly crystallised. 4-Benzyl-3-methyl-*iso*oxazol-5-one (I*b*) (0·2 g.) separated from benzene as needles, m. p. 106°, undepressed when mixed with an authentic specimen, m. p. 107°, prepared according to Schiff and Viciana (*Ber.*, 1897, **30**, 1161; *Gazzetta*, 1897, **27**, 73). When (VI) (2 g.) in 90—95% ethanol (30 ml.) was reduced with hydrogen–platinum (Adams's catalyst) (0·1 g.), hydrogen (244 ml. Calc. for 2 mols., 240 ml.) was absorbed during 4 hours; the resultant solution had a strong ammoniacal odour. Evaporation of the filtered solution *in vacuo* afforded an oil which readily gave crystalline benzylacetone semicarbazone (1·3 g.) which separated from ethanol as needles, m. p. 142°, undepressed on admixture with an authentic sample. The same compound was also obtained by reduction in ethyl acetate. 4-Benzyl-3-methyl*iso*oxazol-5-one (I*b*) did not absorb hydrogen in the presence of palladium, but in presence of a platinum catalyst 1 mole of hydrogen was absorbed with formation of ammonia and benzylacetone. (VI) (2 g.) in anhydrous ethanol (30 ml.) was reduced with hydrogen–platinum, with exclusion of moisture; hydrogen (245 ml. Calc. for 1 mol., 240 ml.) was absorbed during 3 hours and the solution became slightly alkaline but there was no odour of ammonia. Evaporation of the filtered solution *in vacuo* gave an oil (1·9 g.) which gave a purple colour with alcoholic ferric chloride. The oil in ether (20 ml.) was extracted successively with 2% sodium hydrogen carbonate solution (2 × 10 ml.), 2% hydrochloric acid (2 × 10 ml.), and water (10 ml.). Evaporation of the dried solution afforded ethyl α-benzylacetoacetate (1·3 g.), b. p. 165—169°/12 mm. (Leuchs, *Ber.*, 1911, **44**, 1510, gives b. p. 164—165°/12 mm.). The oil (0·5 g.) and concentrated sulphuric acid (3 ml.) were heated on a water-bath for 10 minutes, then cooled, and poured into ice-water (100 ml.); 1-methylindene-2-carboxylic acid (0·25 g.) was obtained as a white precipitate, which separated from ethanol as needles, m. p. 200°, undepressed when mixed with an authentic specimen, m. p. 200°, prepared from ethyl α-benzylacetoacetate and sulphuric acid (von Pechmann, *loc. cit.*; Roser, *loc. cit.*). Acidification of the sodium hydrogen carbonate solution, extraction with ether, and evaporation afforded only a trace of gum, indicating absence of acid. The acid extract when kept for a few hours deposited an oil (0·2 g.) (insoluble in sodium hydrogen carbonate solution), which afforded 1-methylindene-2-carboxylic acid when treated with sulphuric acid and was probably ethyl α-benzylacetoacetate, the basic precursor being presumably ethyl α-benzylacetimidoacetate (II*b*).

3-*Methyl*-4-*anilinomethyl*isoo*xazol*-5-*one* (VIII*a*).—3-Methyl-4-anilinomethylene*iso*oxazol-5-one (VII*a*) (1 g.; Dains and Griffin, *loc. cit.*) in 90—95% ethanol (30 ml.) was reduced in presence of 5% palladium–charcoal (0·1 g.), hydrogen (110 ml. Calc. for 1 mol., 111 ml.) being absorbed in 2 hours. Evaporation of the filtered solution *in vacuo* gave 3-*methyl*-4-*anilinomethyl*isoo*xazol*-5-*one dihydrate* as a pale yellow solid (1 g.) which separated from water as fine pale yellow needles, m. p. 101—102° (decomp.) (Found: N, 11·6. $C_{11}H_{12}O_2N_2,2H_2O$ requires N, 11·65%). This lost water when heated at 50°/1 mm. for 1 hour to give the anhydrous *iso*oxazolone as a very pale yellow powder, m. p. 150°; the anhydrous material was extremely deliquescent (rapidly reverting to the dihydrate in moist air) and coud not be recrystallised satisfactorily, but when it, or the dihydrate, was added to a saturated solution of picric acid in ethanol, the *picrate* was precipitated as a yellow solid which separated from ethanol as prisms, m. p. 167—168° (decomp.) (Found: N, 16·3. $C_{17}H_{15}O_9N_5$ requires N, 16·15%). 3-Methyl-4-anilinomethylene*iso*oxazol-5-one (2 g.) in 90—95% ethanol (40 ml.) was reduced with platinum (0·1 g.), hydrogen (225 ml. Calc. for 2 mols., 222 ml.) being absorbed in 3 hours. Evaporation of the filtered solution (which possessed an ammoniacal odour) *in vacuo* gave almost colourless 4-anilinobutan-2-one, b. p. 149—155°/14 mm. (1·5 g.), which became brown in the air (Found: N, 8·4. Calc. for $C_{10}H_{13}ON$: N, 8·6%). Bayer and Co. (*Zentr.*, 1913, II, 1832) give b. p. 140—145°/10 mm.

3-*Methyl*-4-p-*toluidinomethyl*isoo*xazol*-5-*one* (VIII*c*).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (VII*c*) (1 g.), when reduced with hydrogen–palladium as above, afforded 3-*methyl*-4-p-*toluidinomethyl*isoo*xazol*-5-*one* (0·95 g.) which separated from water as fine, very pale yellow needles, m. p. 181—182° (decomp.) (Found: N, 12·7. $C_{12}H_{14}O_2N_2$ requires N, 12·8%). The *picrate* crystallised from ethanol as prisms, m. p. 167—169° (decomp.) (Found: N, 15·4. $C_{18}H_{17}O_9N_5$ requires N, 15·65%).

3-*Methyl*-4-o-*toluidinomethyl*isoo*xazol*-5-*one* (VIII*b*).—This *product* separated from water as fine pale yellow needles, m. p. 163—164° (decomp.) (Found: N, 12·65%). The *picrate* separated from ethanol as yellow prisms, m. p. 150° (decomp.) (Found: N, 15·45%).

Propiophenone Oxime Acetate (X; R = Et).—Propiophenone oxime (13·5 g.) and acetic anhydride (15 ml.) were heated on the water-bath for 3 hours. Evaporation of the solution *in vacuo* gave an oil which soon crystallised; *propiophenone oxime acetate* (10·5 g.) separated as needles (from light petroleum), m. p. 57° (Found: N, 7·25. $C_{11}H_{13}O_2N$ requires N, 7·35%). The acetate (5 g.) was reduced with hydrogen and platinum (0·2 g.) in ethanol (100 ml.) until 1 mole of hydrogen (585 ml.) had been absorbed, this requiring 5 hours. The filtered solution was evaporated *in vacuo* to afford a pale brown oil, which partly crystallised on being kept overnight. The crystals (1·4 g., 31%) were separated from oil by spreading the mixture over a porous title, and recrystallised from water as needles, m. p. 125°, undepressed when mixed with an authentic sample of propiophenone *N*-acetylimine (XI; R = Et), m. p. 126°.

Hydrogenation of Acetophenone Oxime Acetate (X; R = Me).—The acetate (2 g.) in ethanol (30 ml.) was reduced with platinum (0·1 g.) until 1 mole of hydrogen (252 ml.) had been absorbed (4 hours). Evaporation of the filtered solution gave an oil (1·9 g.). A solution of this in ether was extracted successively with sodium hydrogen carbonate solution, hydrochloric acid, and water; evaporation of the dried ethereal solution gave an oil (1·3 g.) which failed to crystallise. The oil (1 g.) was boiled under reflux with N-hydrochloric acid (10 ml.) for 30 minutes, and the cooled solution extracted with ether (20 ml.). Evaporation of the extract afforded acetophenone (0·5 g.) (2 : 4-dinitrophenylhydrazone, m. p. 248°, undepressed when mixed with an authentic specimen, m. p. 250°). The aqueous solution was evaporated to a small volume and made alkaline with 5N-sodium hydroxide, whereupon ammonia was evolved; neutralisation of the solution and addition of ferric chloride produced a red colour, and boiling the mixture precipitated basic ferric acetate.

Oxidation of Propiophenone N-*Acetylimine* (XI; R = Et).—A solution of the acylketimine (1 g.) in acetone (100 ml.) was boiled under reflux, and solid potassium permanganate added until a lasting pink colour was obtained (about 3 g. were required). The solution was filtered, the filtrate decolorised with sulphur dioxide and re-filtered, and the filtrate evaporated to dryness *in vacuo*, to yield crystalline *N*-acetylbenzamide (0·8 g.) which separated from water as laths, m. p. 116°, undepressed when mixed with an authentic specimen, m. p. 116° (Titherley and Holden, *J.*, 1912, **101**, 1880). The filtrate from the above crystallisation had an odour of benzaldehyde and gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235°, thereof.

Technical College, Sydney, N.S.W., Australia.

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147. *Crossed Reaction Chains in Oxidation by Molecular Oxygen. Part I. Oxidation of Hydrocarbons in Aldehyde–Air Mixtures.*

By N. J. H. Small and A. R. Ubbelohde.

One theory of hydrocarbon oxidation assumes that the reaction chain

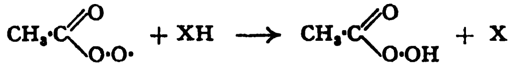
$$R + O_2 \longrightarrow RO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RO_2 + RH \longrightarrow RO{\cdot}OH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

is closely similar whether R is an alkyl radical in the oxidation of hydrocarbons, or an acyl radical in the oxidation of aldehydes.

To test how far the oxidation chains for these two molecular species can in fact "cross," small proportions of paraffins, olefins, benzene, and hydrogen have been added to an acetaldehyde–air mixture undergoing vigorous oxidation around 150—200°. These added molecules were found either to be substantially inert, or to act as inhibitors for the oxidation of the acetaldehyde.

The conclusion is that the oxidation chains of the hydrocarbon tested cannot "cross" freely with those for acetaldehyde, at the temperature of the experiment. When the added molecules act as inhibitors for the oxidation of acetaldehyde, they may do so by donation of hydrogen atoms to the peroxide radicals :



$$CH_3{\cdot}C(=O)O{\cdot}O{\cdot} + XH \longrightarrow CH_3{\cdot}C(=O)O{\cdot}OH + X$$

but the resulting X radicals do not themselves continue long oxidation chains under the conditions used. The inhibiting action of hydrogen may also be caused by its deactivating "energy chains" by facilitating the exchange of vibrational energy.

The close relation between the oxidation mechanism of gaseous aldehydes and that of gaseous paraffins has been noted by various authors, and has been used to elucidate some of the steps in hydrocarbon oxidation (Ubbelohde, *Proc. Roy. Soc.*, *A*, 1935, **152**, 354, 378; Lewis and Von Elbe, "Flames, Combustion and Explosions of Gases," Cambridge, 1938).

One of the outstanding difficulties in substantiating the details of a scheme of oxidation for gaseous hydrocarbons is that the minimum temperature at which reaction can conveniently be observed at ordinary pressures is around 250°. At this temperature, labile reaction products such as hydroperoxides, whose constitution is particularly significant, are frequently too short-lived for identification except by special techniques (Egerton, Llewellyn Smith, and Ubbelohde, *Phil. Trans.*, 1935, **234**, 433; Ubbelohde, Drinkwater, and Egerton, *Proc. Roy. Soc.*, 1936, **158**, No. 878, 103). The guiding idea in the researches to be described is to discover which of the numerous reaction steps in the oxidation of hydrocarbons imposes the use of temperatures as high as 250°. In particular, the aim was to investigate how far the reaction rate was controlled by the postulated initial attack on the hydrocarbon

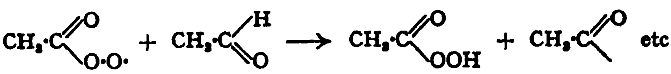
$$X + RH \longrightarrow XH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

where X may be any third body; in the main oxidation chain X is a peroxide radical (cf. Ubbelohde *et al.*, *locc. cit.*), *i.e.*,

$$R + O_2 \longrightarrow RO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$RO_2 + RH \longrightarrow RO{\cdot}OH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The experimental principle employed was to bombard the RH molecule with a large number of aldehyde peroxide radicals, at a temperature where the reaction



$$CH_3{\cdot}C(=O)O{\cdot}O{\cdot} + CH_3{\cdot}C(=O)H \longrightarrow CH_3{\cdot}C(=O)OOH + CH_3{\cdot}C(=O)- \text{ etc.} \quad . \quad . \quad . \quad (3)$$

is proceeding freely, and to investigate :

(*a*) Whether the result of the attack was to start *hydrocarbon* oxidation chains according to (1) and (2) above;

(*b*) Failing the establishment of such chains, whether there was any evidence for the formation of alkyl radicals under the initial bombardment of hydrocarbon by aldehyde peroxide radicals, according to reaction (*A*), but without extensive sequences of (1) and (2); and

(*c*) Failing either (*a*) or (*b*), whether there was any evidence of chemical crossing of reaction chains at the temperature of the experiment.

Possibility (*a*) would have the great practical advantage of permitting the controlled oxidation of hydrocarbons in the vapour phase at much lower temperatures than usual; this could lead to interesting and valuable oxidation intermediates.

Possibility (*b*) would be of very considerable theoretical interest, as indicating new facts about the kinetic characteristics of the oxidation steps for paraffins. The yields of interesting oxidation intermediates would, however, be much smaller since proportionally many fewer paraffin molecules would enter into reaction for each R radical formed according to (*A*).

Finally, possibility (*c*) would imply the need for very considerable activation energy, even for reaction (*A*).

As is discussed below, the main conclusion was that none of the hydrogen compounds so far exposed to bombardment by acetaldehyde peroxide radicals appears to undergo reaction according to (*a*). Heptane, hydrogen, and hex-1-ene give definite evidence of following course (*b*). This has theoretical as well as practical implications which are further detailed below.

EXPERIMENTAL.

Experimental Procedure.—The main lines of experimental procedure can be summarised by reference to Fig. 1. *A*—*B* is a Pyrex reaction tube, 50 cm. long, of internal diameter 4·5 cm., wound with nichrome wire and lagging, and heated electrically so as to maintain the gas flowing through it at any temperature up to approx. 360°. At the inner ends of *a, b, c*, broken glass fragments and glass wool serve to produce turbulence so as to mix the gas streams. Normally one of these is pure nitrogen charged to a calculated partial pressure with acetaldehyde vapour. A second is air, which could be used to carry the XH molecules if these were required in the oxidation. The total flow in mols./sec. was not appreciably affected when the second stream was carrying molecules of a compound XH (see Table I). For mixing in hydrogen or additional nitrogen (Table I *b*), a third stream was introduced as indicated in Fig. 1 (*c*).

TABLE I.

Mixture.	$CH_3\cdot CHO$.	XH.	O_2.	N_2.	Total rate of flow.	Temp. of steep rise of oxidation rate.
a, $CH_3\cdot CHO$/(ref. O_2/N_2 mixture) ...	0·267	—	0·0937	0·803	1·164	150°
b, ,, + N_2 *	0·267	0·142 *	0·0937	0·803	1·306	190
c, ,, + C_6H_6	0·267	0·0982	0·0937	0·803	1·262	190
d, ,, + C_6H_{14}	0·267	0·142	0·0937	0·803	1·306	190
e, ,, + C_7H_{16}	0·267	0·100	0·0937	0·803	1·264	200
f, ,, + H_2	0·267	0·150	0·0937	0·803	1·314	210
g, ,, + unsaturated	0·267	0·125	0·0937	0·803	1·289	*ca.* 200

* Additional N_2 in this mixture matches approx. the amount of XH in mixtures *c* to *g*.
Figures are in 10^{-3} g.-mols./sec.

By this means a mixture of acetaldehyde and (nitrogen + XH) in approximately constant molar proportions flowed through the reaction tube at constant velocity. The aim was to maintain substantially constant conditions for the aldehyde oxidation, except in so far as these were modified by the crossing of the aldehyde reaction chains with any reactions involving XH.

At *B* the condensing system was maintained at the temperature of liquid oxygen, the cold finger shown in Fig. 1 being cooled by means of carbon dioxide and alcohol. As required, this condensation vessel could be rapidly interchanged with similar vessels, so as to permit collection of a series of samples without any interruption in the reaction flow. The products were allowed to melt and were analysed as described below.

The reactions and the melting of the reaction products were carried out behind protective screens, since when oxidation is extensive very considerable yields of peroxide might be formed. Actually only mild ignitions were observed from time to time when combustion was in progress.

A cross piece fitted with quartz windows was also provided in the reaction system near *A*. This was for use in experiments on photochemical initiation described in subsequent publications, but will not be referred to again in the present paper.

Experimental Details.—Gases were taken from cylinders of compressed air and nitrogen at rates controlled by capillary flow meters with mercury manometers. Stream (*a*) (approx. 10 c.c./sec.) was nitrogen saturated at 0° with acetaldehyde vapour and shielded from strong light. Stream (*b*) consisted of air normally saturated with various molecules XH by maintaining the appropriate liquid in a pair of carburettors at the calculated temperatures. A third stream (*c*) was used for the compositions (*b*) and (*f*) in Table I. This gave approximately constant composition, as is shown in Table I.

Details of the carburettors are illustrated in Fig. 2. Tests showed that with carburettors in series no increase in their number beyond two further increased the content of the gas in aldehyde or in XH, *i.e.*, saturation was effectively attained.

Temperature control in the baths around the carburettors was by an immersion heater regulated by a Sunvic control.

Materials.—*Acetaldehyde.* This was prepared by distilling paraldehyde with dilute sulphuric acid as required, using a current of nitrogen to protect it from oxidation.

Benzene, f. p. 5·48°. This was prepared by repeated crystallisation of " AnalaR " benzene, thiophen-free. It was used with the carburettor vessel at 50·5° to give a partial pressure of 280 mm.

n-*Heptane*. This was prepared by fractionating commercial heptane and collecting the cut of b. p. 95·5—97°. Before fractionation unsaturated hydrocarbons were carefully removed on account of their suspected action as inhibitors. The crude heptane was stored over fuming oleum for about a week with occasional shaking. It was then repeatedly washed with strong potassium hydroxide solution and then with water, and dried (Na_2SO_4) for 24 hours. Carburettors at 68° gave p = 280 mm.

n-*Hexane*. This was prepared in the same way as *n*-heptane. The final cut had b. p. 67·5—68·5°. Both fractionations were carried out in nitrogen. Carburettors at 41° gave a partial pressure of 280 mm.

n-*Hex*-1-*ene*. This was prepared by dehydrating *n*-hexyl alcohol by the procedure recommended in *Org. Synth.*, Vol. I, p. 421. The fraction of commercial *n*-hexyl alcohol, b. p. 155·2—156·0°, was dehydrated with 50% aqueous sulphuric acid, and the hydrocarbon was repeatedly washed with concentrated sodium hydroxide solution and then refluxed for 24 hours with two successive batches of 20% aqueous sodium hydroxide solution to remove any trace of sulphur compounds.

Final drying (Na_2SO_4) and fractionation through a column gave a cut of b. p. 61—64°. No trace of sulphur compounds was detected in the product. This material was mixed with twice its volume of *n*-hexane and used with carburettors at 41° to give p = 280 mm.

FIG. 1.

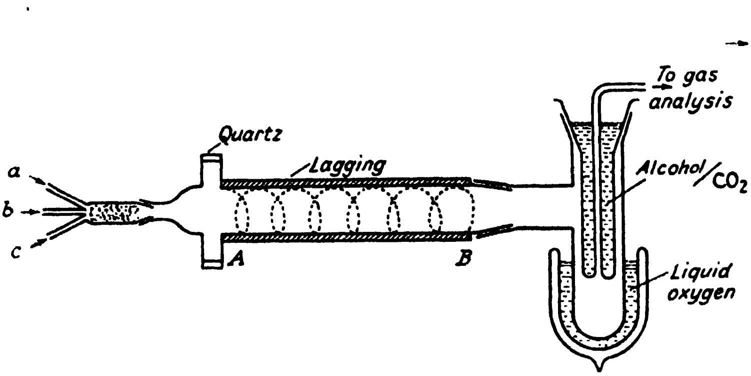
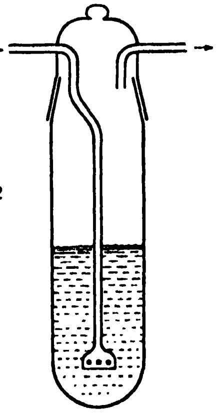


FIG. 2.



Combustion apparatus and vapourisers.

Hydrogen. Taken from cylinders, this was used without further purification. Its rate of flow was determined by a separate flowmeter and was adjusted to a value such that the amount of hydrogen passing through the combustion tube was comparable to the concentration of molecules XH used in previous experiments.

Preparation of the Reaction Vessel.—Before each run, the reaction vessel was cleaned with hot nitrating acid at about 80°, then with abundant distilled water, and finally dried with filtered air. The temperature was measured by a thermometer reading to 360° ± 0·5° and wholly encased in a Pyrex tube which was likewise cleaned with nitrating acid etc. before each run. The degree of reproducibility thus achieved was good, as can be inferred, for example, from the results on the oxidation of pure acetaldehyde (Figs. 3 and 4).

Collection and Analysis of Products.—Only summarised results will be given in the present paper.

The amounts of acetaldehyde, XH, and oxygen used in a run were determined by analysis and checked from the amounts remaining in the calibrated carburettors and the volumes of gases used. The gases flowing past the cooled surfaces were normally stripped of all except permanent gases and possibly some carbon dioxide. Completeness of condensation was verified, for example, by the obtaining of negative tests for acetaldehyde and formaldehyde during the progress of a run. When the percentage content of carbon dioxide was required, samples of exit gases were collected without the condensing system in place. Exit gases were analysed by a " fountain " gas-analysis apparatus which need not be detailed here.

The treatment of the melted condensate was as follows: As a precautionary measure, 25 c.c. of distilled water were first added, to dilute any peroxides formed. When hydrocarbon had been added the condensate separated into two layers. The hydrocarbon layer was shaken 4—5 times with water, and the washings were added to the aqueous layer. The whole aqueous product was made up as a standard solution which could be titrated for peroxide, acid, and aldehyde content (see below).

In the case of *n*-heptane, recovered hydrocarbon, after being scrubbed with water, was carefully fractionated to obtain a preliminary idea of the fate of the molecules of XH which had reacted. Not more than 1% of the *n*-heptane had given rise to oxidation products of comparable molecular weight.

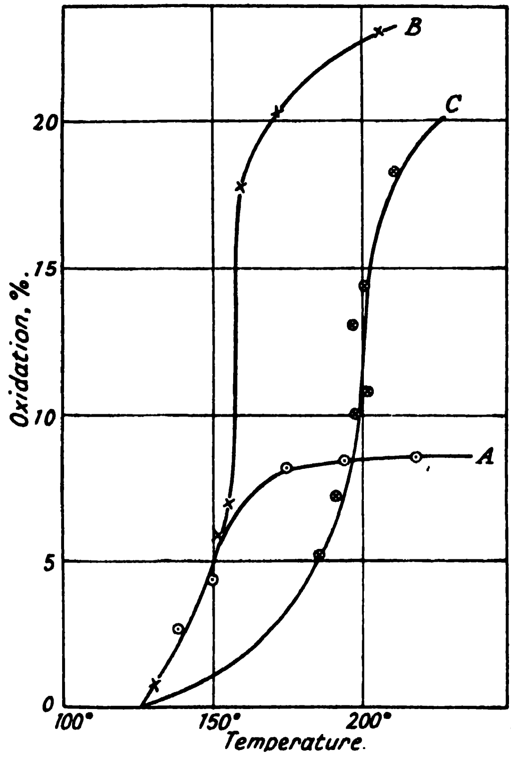
More detailed investigation of what happens to those molecules of XH which are attacked whilst passing through the reacting aldehyde–oxygen system requires special techniques, in view of the small amounts involved. This is being described in subsequent papers.

Fine needle-like crystals were also isolated from the residues of fractionation. Qualitative tests showed this to be a polymerisation product of acetaldehyde. That it is probably metaldehyde seems to be confirmed (i) by m. p. *ca.* 125° and (ii) by the fact that heating them with a drop of dilute acid yielded acetaldehyde.

The aqueous layer contained unchanged acetaldehyde, formaldehyde, peroxides, and acids (chiefly acetic and peracetic).

FIG. 3.

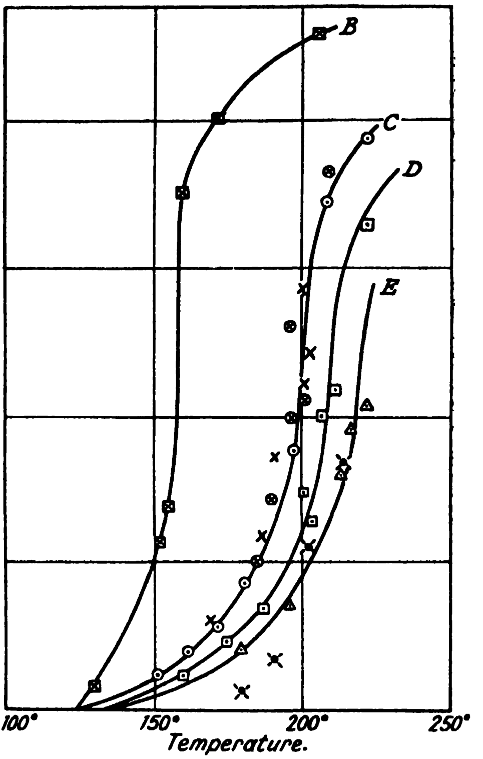
Effect of aldehyde/O_2/N_2 ratio on the critical oxidation temperature of acetaldehyde.



× *Fuel/O_2/N_2 ratio* = 2·8 : 1 : 8·57.
⊙ *Fuel/O_2/N_2 ratio* = 1 : 1 : 6.
⊕ *Fuel/O_2/N_2 ratio* = 2·8 : 1 : 8·57
+ *added* N_2.

FIG. 4.

Effect of added molecules on the critical oxidation temperature of an aldehyde/ O_2/N_2 mixture 2·8 : 1 : 8·57.



☒ *Reference mixture Ald./O_2/N_2* 2·8 : 1 : 8·57.
× " " + *added benzene.*
⊗ " " + *added nitrogen.*
⊙ " " + *added hexane.*
⊡ " " + *added heptane.*
△ " " + *added hydrogen.*
✖ " " + *unsaturated.*

The peroxides were determined by filling conical flasks, containing aliquot portions of the scrubbing water with carbon dioxide, adding potassium iodide and dilute sulphuric acid, and allowing reaction to proceed for 2 minutes before titration with standard sodium thiosulphate solution. Prompt analysis of the peroxides was necessary after the melting of the condensate, since the concentration of peroxides in the scrubbing liquor decayed to one-half in *ca.* 15 minutes. This decay could be delayed by addition of free acid to the scrubbing water. In the experimental results given below, the data for peroxides were generally obtained within 2—3 minutes of melting of the condensate. They are believed to be fairly close to the initial concentrations present, unless the decay on condensation or on melting is much more rapid than the average estimated for the samples made up.

Acids formed were titrated with N-sodium hydroxide (phenolphthalein).

The total aldehyde content was analysed by means of sodium sulphite (cf. Walker, "Formaldehyde," 1944, p. 257) using thymolphthalein as indicator and titrating the alkali produced with N-sulphuric acid. Where required, formaldehyde was determined separately by the method used by Egerton, Smith, and Ubbelohde (*loc. cit.*). Addition of an equal volume of 10% sulphuric acid to the test solution suppresses the reaction of the higher aldehydes with Schiff's reagent and makes it specific for the determination of formaldehyde. The acetaldehyde which is present in appreciably greater amounts gives an immediate colour, but this fades in ½ hour, whereas that due to formaldehyde does not fade in 12 hours.

During the analysis the purple tint due to the formaldehyde present was compared colorimetrically with that produced by a standard solution, and the result is included in the table below.

Results.—(a) *Oxidation of pure* n-*heptane and pure* n-*hexane.* In confirmation of previous results, experiments which need not be recorded in detail showed that when various mixtures of these paraffins with oxygen and nitrogen in proportions similar to those in Table I were passed through the apparatus without acetaldehyde, the minimum temperature at which appreciable oxidation could be detected under the most favourable conditions was 250°. Products included peroxides and much formaldehyde.

(b) *Formation of acids and peroxides.* With acetaldehyde mixtures, the dominant reaction either alone or in the presence of XH was in all cases the oxidation of the acetaldehyde. Curves in Figs. 3 and 4 show plots of the aldehyde oxidised to peroxide and acid. The sum of the g.-equivs. of these two constituents produced under different conditions is expressed as a percentage of the acetaldehyde originally present in the reaction mixture. Smooth plots are obtained with a steep rise at a critical temperature which depends on the mixture used and on any inhibiting effects due to XH. For convenience these temperatures are listed in the last column of Table I.

(c) *Other oxidation products of acetaldehyde.* Representative gas analyses are given in Table II. It will be observed that at the temperature of the experiment both carbon monoxide and dioxide are detectable in the exit gases, the former in greater quantity. Other oxidation products of higher molecular weight are referred to above.

TABLE II.

Representative gas analysis (reaction tube, 200°. Mixture I*a*).

Material.	Supplied.	Recovered.	Material.	Supplied.	Recovered.
Acetaldehyde	1·23 g.-equiv.	0·155 g.-equivs.	Formaldehyde	—	0·022 g.-equivs.
Oxygen	0·241 g.-equivs.	0·029 g.-mols.	Peroxide	—	0·085 „
CO_2	—	0·0156 „	Acid	—	0·135 „
CO	—	0·029 „			

(d) *Oxidation of heptaldehyde by acetyl peroxide radicals.* As an addition to determination of the effect of added molecules on acetaldehyde oxidation (Table I), heptaldehyde was introduced into an aldehyde oxidation at 200° (carburettors at 104°). About half of it could be recovered under these conditions, the remainder being apparently oxidised. If the formation of the corresponding aldehyde is an early step in hydrocarbon combustion, then the observations in the previous paragraph suggest that, when the paraffin reacts, the corresponding aldehyde should be recoverable A preliminary fractionation of *n*-heptane collected after passage through the oxidising aldehyde system gave no evidence of heptaldehyde formation. Further comment is reserved until larger quantities can be investigated.

DISCUSSION.

(1) *Characteristics of the Oxidation of Acetaldehyde.*—In accordance with the results of other workers (cf. McDowell and Thomas, *J.*, 1949, 2208, for recent references) curves *A* and *B* of Fig. 3 confirm that the oxidation of acetaldehyde proceeds at markedly lower temperatures and more rapidly for a fuel–air mixture of 2·8 : 1 than of 1 : 1. The yields of acid and peroxide (calculated as acetic and peracetic acids) correspond with about 20% of the aldehyde actually consumed in passage through the reaction tube. Gas analysis (cf. Table II) shows the presence of some carbon monoxide and dioxide, as well as giving information on the amount of oxygen consumed. Although the oxygen is all accounted for, it is not clear what happens to the unrecovered acetaldehyde. Some of it polymerises to a rubber-like polymer which can be depolymerised on storage or boiling with water.

(2) *Effect of Hydrocarbons on the Oxidation of Acetaldehyde.*—From Fig. 4 and Table I, it is evident that the added hydrocarbon XH inhibits the oxidation of acetaldehyde, when XH is hydrogen, hexene, or heptane.

The order of increasing collision diameters (Table III) does not suggest any explanation of this inhibition in terms of a simple dilution effect.

TABLE III.

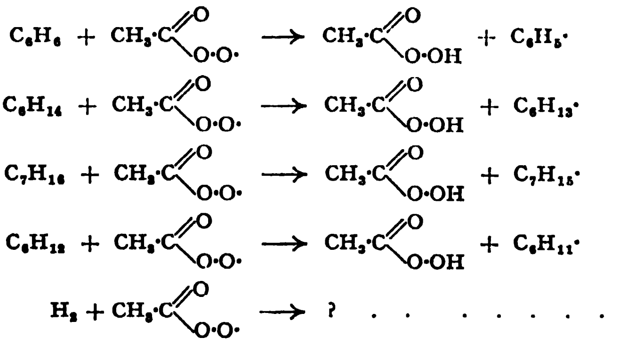
Molecule	C_6H_6.	N_2.	H_2.	C_6H_{14}.	C_7H_{16}.
Collision diameter, A.	4·66	3·18	2·40	5·18	5·8

Cf. Schuil, *Phil. Mag.*, 1939, **28**, 683.

When inhibition is observed it could in principle arise either by energy degradation on collision between the inhibitor and the activated chain carriers, or by chemical reaction between the inhibitor and the chain carrier. The possibility of energy degradation is discussed under

(3), but in the authors' opinion the inhibition can most readily be interpreted on the theory that acetyl peroxide radicals have a finite probability of removing hydrogen from each of the molecules XH, but with varying effectiveness. An order of increasing ease of removal would be as in *A* (i) to *A* (v) below.

From Fig. 4 it appears that the molecules nitrogen, benzene, and hexane behave substantially in the same way and may be presumed to be inert on collision with acetyl peroxide radicals. However the fact that heptane and hexene both have marked inhibitory effects could be reconciled with the apparent inertness of hexane and benzene if the probability of removal of hydrogen in the reactions *A*(i) and *A*(ii) is markedly less than that in *A*(iii) and *A*(iv). Comparatively small differences in activation energy would suffice to give this effect. For example, if the activation for *A*(ii) were 6 kcals. greater than for *A*(iii), and the temperature-independent terms in the velocity equation were the same, the rate of *A*(ii) would be one-thousandth of the rate of *A*(iii) at 460° K.



$$C_6H_6 + CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}O{\cdot}}{\lessgtr}}} \longrightarrow CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}OH}{\lessgtr}}} + C_6H_5{\cdot} \qquad \ldots \quad A\text{(i)}$$

$$C_6H_{14} + CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}O{\cdot}}{\lessgtr}}} \longrightarrow CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}OH}{\lessgtr}}} + C_6H_{13}{\cdot} \qquad \ldots \quad A\text{(ii)}$$

$$C_7H_{16} + CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}O{\cdot}}{\lessgtr}}} \longrightarrow CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}OH}{\lessgtr}}} + C_7H_{15}{\cdot} \qquad \ldots \quad A\text{(iii)}$$

$$C_6H_{12} + CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}O{\cdot}}{\lessgtr}}} \longrightarrow CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}OH}{\lessgtr}}} + C_6H_{11}{\cdot} \qquad \ldots \quad A\text{(iv)}$$

$$H_2 + CH_3{\cdot}C{\overset{\textstyle O}{\underset{\textstyle O{\cdot}O{\cdot}}{\lessgtr}}} \longrightarrow \; ? \qquad \ldots \ldots \ldots \quad A\text{(v)}$$

The hypothesis is that, when the reactions occur, the oxidation is inhibited because the new radicals produced fail to prolong the chains. As the temperature is raised oxidation proceeds once more, so that the inhibition is compensated. In principle this could happen either by further oxidation of aldehyde or by more important contributions to the overall oxidation from (1) and (2). So far as it has been possible to examine the condensates it seems unlikely that extensive chain oxidation of any of the hydrocarbons occurs, even at the critical reaction temperatures listed in Table I. The inference is that even when alkyl radicals are produced by reaction (*A*) it requires a higher temperature before chain oxidation of the hydrocarbon will occur at all freely. Thus *either* step (1) *or* step (2) must have an activation energy which requires the temperature of 250° before a pure paraffin will be oxidised at all freely.

What actually happens to the hydrocarbon radicals in the present set-up is still under investigation, but clearly they do not start the long oxidation chains which apply at 250° or above. It is significant that *A*(iv) occurs much more readily than *A*(ii), presumably owing to the smaller activation required to remove hydrogen atoms from the α-position relative to a double bond in an olefin, compared with the activation to remove hydrogen atoms from a paraffin (cf. Farmer, *Trans. Faraday Soc.*, 1942, **38**, 348).

(3) *Inhibition of Acetaldehyde Oxidation by Molecular Hydrogen.*—This striking effect may be akin to the inhibition of oxidation of pentane by molecular hydrogen in the region 260—280° (Prettre, *Compt. rend.*, 1936, **203**, 619. Jost (" Explosion and Combustion Processes in Gases," McGraw-Hill, 1946) has attributed this effect of hydrogen to its catalytic influence on the reaction walls. An alternative explanation may well be that energy chain transfers are important in these oxidations (Ubbelohde, *Proc. Roy. Soc.*, 1935, *A*, **152**, 369). The well known effect of hydrogen in degrading the vibrational energy by collision with carbon dioxide molecules (cf. the review in *Reports Progr. Physics*, 1948, **12**, 264) may be paralleled by its effect in degrading the vibrational energy of chain carriers before these have time to continue the succeeding links in the chain.

A third possible explanation would be that the acyl peroxide radicals use up both hydrogen atoms on collision, so that the chain is not propagated in the usual way.

QUEENS UNIVERSITY, BELFAST.

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148. *Acenaphthene Series. Part III. Orientation of* tert.*-Butyl- and Di-*tert.*-butyl-acenaphthene, and Preparation of New Derivatives.*

By H. E. Nürsten and A. T. Peters.

The butylation of acenaphthene by means of *tert.*-butyl chloride and aluminium chloride, in carbon disulphide as a solvent, is shown to yield 2-*tert*-butylacenaphthene and 2 : 5-di-*tert.*-butylacenaphthene.[*] The orientation of these hydrocarbons is based mainly on their oxidation to benzene-1 : 2 : 3 : 5-tetracarboxylic acid and provides the first instance of direct substitution of the acenaphthene nucleus in the 2-position.

The alkylacenaphthenes are degraded to the corresponding alkylnaphthalenes and thus a hydrocarbon, first described in 1884, has been identified as 2 : 7-di-*tert.*-butylnaphthalene.

New derivatives of 2-*tert.*-butyl- and of 2 : 5-di-*tert.*-butyl-acenaphthene are prepared.

The butylation of acenaphthene was first recorded in Part I of this series (Peters, *J.*, 1942, 562), where the reaction between a solution of the hydrocarbon in carbon disulphide and *tert.*-butyl chloride, in presence of aluminium chloride, was described. The separation of *tert.*-butylacenaphthene from the parent hydrocarbon and from the disubstituted product was a tedious process, but eventually the monoalkylacenaphthene was obtained in a small yield, but very pure, having m. p. 88—88·5°, whereas m. p. 73—74° had been recorded previously. Buu-Hoï and Cagniant (*Rev. sci.*, 1943, **81**, 72) gave m. p. 72° for *tert.*-butylacenaphthene, which they obtained in very poor yield from the products of a similar reaction without the use of a solvent.

Orientation of tert.*-Butylacenaphthene.*—Those substitution reactions of acenaphthene which lead to products that have been orientated (35 studies) are summarised in the table.

Acenaphthene is generally attacked in the 3-position, rarely in the 1-position, never in the 2-position, and in the 7-position only by oxidising agents. Some 2-substitution had been postulated but not proved in the case of benzylation.

From consideration of these results, the butylation of the hydrocarbon was expected to yield 3-*tert.*-butylacenaphthene, which orientation was accepted in Part I and by Buu-Hoï and Cagniant.

In the present research, the *tert.*-butylacenaphthene was converted into *tert.*-butylnaphthalic anhydride and this was decarboxylated to 2-*tert.*-butylnaphthalene either by distillation with soda–lime at ordinary or reduced pressure, or by mercuration and decomposition, followed by treatment with copper-bronze in boiling quinoline. The 2-*tert.*-butylnaphthalene was shown to be identical with that synthesised unambiguously by Bromby, Peters, and Rowe (*J.*, 1943, 144). This result indicated that the starting material had been 2(or 1)-*tert.*-butylacenaphthene. However, Tsukervanik and Terentieva (*J. Gen. Chem. Russ.*, 1937, **7**, 637) stated that 1-alkylnaphthalenes isomerise on heating to 2-alkylnaphthalenes and their statement received some support from Mayer and Schiffner (*Ber.*, 1934, **67**, 67) and from Cullinane and Chard (*Nature*, 1948, **161**, 690), although these workers employed temperatures above 400° and catalysts. The reaction might therefore be explained by 3-*tert.*-butylacenaphthene yielding 1-*tert.*-butylnaphthalene, which subsequently isomerised. No support could be found for this course of the degradation, for even when carried out under reduced pressure the reaction gave 2-*tert.*-butylnaphthalene only.

In spite of the negative results previously recorded, it was again attempted to oxidise *tert.*-butylnaphthalic anhydride, and benzene-1 : 2 : 3 : 5-tetracarboxylic acid was obtained by means of nitric acid under pressure. It was thus proved conclusively that the butylation of acenaphthene had yielded 2-*tert.*-butylacenaphthene. No rearrangement had therefore occurred in the degradation of this hydrocarbon to 2-*tert.*-butylnaphthalene.

The butylation of acenaphthene therefore presents the first example of direct 2-substitution therein. The abnormal orientation of the product is in agreement with the abnormal orientation frequently observed in the products of Friedel–Crafts alkylations in the benzene series (*e.g.*, Ador and Rilliet, *Ber.*, 1878, **11**, 1627; Kelbe, *Annalen*, 1881, **210**, 1; Pajeau, *Bull. Soc. chim.*, 1945, **12**, 637; Essner and Gossin, *ibid.*, 1884, **42**, 213; Fournier, *ibid.*, 1892, **7**, 651; Heise and Töhl, *Annalen*, 1892, **270**, 155). Moreover, naphthalene is generally attacked in

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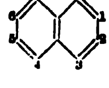
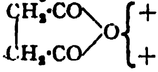
[*] Richter's numbering of the acenaphthene system is used in this paper. The orientation of many of these compounds amends that in Parts I and II.



the β-position in Friedel–Crafts alkylations (*e.g.*, Roux, *Bull. Soc. chim.*, 1884, **41**, 379; *Ann. Chim. Phys.*, 1887, **12**, 289).

Reagent.	Position of substitution.
HNO_3 + AcOH	3 [1,2]
Ph·CO·NO_3 or NO(OH)$(OAc)_2$	1, 3 (*ca.* 0·03% in 2) [3]
Cl_2	3 [4–7]
SO_2Cl_2	3 [7]
Br_2	3 [1,5]
I_2 and HgO	5 [5,6]
H_2SO_4 or Cl·SO_3H at 0°	3 [8,9]
H_2SO_4 at 100°	1 [8]
AcCl + $AlCl_3$	3, 1 (little) [1,10]
HOAc + HF	1 (up to 84%), 3 [10,11]
CH_2Cl·COCl + $AlCl_3$	3, 1 [12,13]
CH_2Br·COBr + $AlCl_3$	3 [14]
CH_2(CN)·COCl + $AlCl_3$	3 [15]
Et·COCl + $AlCl_3$	3, 1(?) [16,14]
CH_3·CH:CH·COCl + $AlCl_3$	3 [10]
 +$AlCl_3$	3 (78%), 1 (15%) [17]
+HF	1, 3 [10]
Maleic anhydride + $AlCl_3$	3 [17]
Ph·COCl + $AlCl_3$	3 [1]
CH_2Ph·COCl + $AlCl_3$	3 [18,19]
CH_2Ph·CO_2H + HF	3, 1 [19]
$C_6H_4(CO)_2O$ + $AlCl_3$	3 [1,20]
NH_2·COCl + $AlCl_3$	3 [21,12]
$(COCl)_2$	3 [22]
Phenylethyluronium chloride + $AlCl_3$	3 [23]
CNBr + $AlCl_3$	3 [24,25]
CH_2O + P_2O_5	3 [26]
$COCl_2$ + $AlCl_3$	3 [26]
HCN or H·C(NH)·N:CHCl + $AlCl_3$	3 [27,28]
H·CONMePh + $POCl_3$	3 [28]
EtBr + $AlCl_3$	3(?) [29]
CH_2PhCl + $ZnCl_2$, etc.	3, 2(?) [30–32]
PbO_2 + HOAc	7 [33]
$Pb(OAc)_4$ + HOAc at 60—70°	7 [34–37]
Cl_2 or Br_2 in sunlight	7 [38]

References.—[1] Graebe, *Annalen*, 1903, **327**, 77. [2] Rowe and Davies, *J.*, 1920, **117**, 1344. [3] Morgan and Harrison, *J. Soc. Chem. Ind.*, 1930, **49**, 413T. [4] Crompton and Cyriax, *Proc.*, 1908, **24**, 241. [5] Sachs and Mosebach, *Ber.*, 1910, **43**, 2473. [6] Crompton and Walker, *J.*, 1912, **101**, 958. [7] Dziewonski and Zakrzewska-Baranowska, *Bull. Acad. Polonaise*, 1927, *A*, 65. [8] Dziewonski and Kocwa, *ibid.*, 1926, *A*, 209; see also *ibid.*, 1927, *A*, 65; 1928, *A*, 405, 507. [9] Bogert and Conklin, *Coll. Czech. Chem. Comm.*, 1933, **5**, 187. [10] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272. [11] Mowry, Renoll, and Huber, *ibid.*, 1946, **68**, 1105. [12] G.P. 479,916; Friedlaender, **16**, i, 516. [13] Lyashchenko, Sokolova, and Zelinskii, *J. Gen. Chem. Russ.*, 1941, **11**, 1001. [14] Nightingale, Ungnade, and French, *J. Amer. Chem. Soc.*, 1945, **67**, 1262. [15] G.P., 536,652, 544,886, 547,643, 556,659; Friedlaender, **18**, i, 612, 619, 620; **19**, ii, 2179, respectively. [16] Dziewonski and Moszew, *Bull. Acad. Polonaise*, 1931, *A*, 158. [17] Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 4347. [18] Päpcke, *Ber.*, 1888, **21**, 1331. [19] Fieser and Kilmer, *J. Amer. Chem. Soc.*, 1940, **62**, 1354. [20] Peters and Rowe, *J. Soc. Dyers Col.*, 1943, **59**, 52. [21] Gattermann, *Annalen*, 1888, **244**, 29. [22] Liebermann and Zsuffa, *Ber.*, 1911, **44**, 202. [23] U.S.P. 2,072,237. [24] Karrer, Rebman, and Zeller, *Helv. Chim. Acta*, 1920, **3**, 261. [25] Grignard, Bellet, and Courtot, *Ann. Chim.*, 1915, **4**, 28. [26] Dziewonski, Kahl, Koczorowska, and Wulffsohn, *Bull. Acad. Polonaise*, 1933, *A*, 194. [27] Hinkel, Ayling, and Beynon, *J.*, 1936, 339. [28] Fieser and Jones, *J. Amer. Chem. Soc.*, 1942, **64**, 1666. [29] Mayer and Kaufmann, *Ber.*, 1920, **53**, 289. [30] Dziewonski and Rychlik, *Ber.*, 1925, **58**, 2239; Dziewonski and Leonhard, *Bull. Acad. Polonaise*, 1928, *A*, 99. [31] Lal, *J. Indian Chem. Soc.*, 1935, **12**, 616. [32] Sharma and Dutt, *ibid.*, p. 774. [33] Marquis, *Compt. rend.*, 1926, **182**, 1227. [34] Monti, *Gazzetta*, 1938, **68**, 608. [35] Fieser and Cason, *J. Amer. Chem. Soc.*, 1940, **62**, 432. [36] Brown and Yee, *ibid.*, 1945, **67**, 874. [37] Fieser and Putnam, *ibid.*, 1947, **69**, 1041. [38] Jones, *J. Soc. Chem. Ind.*, 1949, **68**, 225.

1-*tert.*-Butylacenaphthene, a liquid, b. p. 155—160°/0·8 mm., was synthesised by Buu-Hoï and Cagniant (*Rev. sci.*, 1942, **80**, 176) and was therefore quite different from the hydrocarbon under discussion.

*Orientation of Di-*tert.*-butylacenaphthene.*—By analogy with the other reactions of acenaphthene and of monosubstituted acenaphthenes, it had been assumed that the di-*tert.*-butylacenaphthene formed in the butylation of acenaphthene had the 3 : 4-structure. However, di-*tert.*-butylacenaphthene was easily oxidised by sodium dichromate in boiling acetic acid to di-*tert.*-butylnaphthalic anhydride, which by means of nitric acid under pressure was converted into benzene-1 : 2 : 3 : 5-tetracarboxylic acid. Here, as in the case of the *tert.*-butylnaphthalic anhydride, relatively high concentrations of nitric acid could be used in the oxidation, as the carbonyl groups deactivated the nucleus sufficiently to prevent nitration. The formation of benzene-1 : 2 : 3 : 5-tetracarboxylic acid proved that at least one *tert.*-butyl group of di-*tert.*-butylacenaphthene is *meta* to the acenaphthene bridge and that one such group is in each ring of the naphthalene nucleus.

Mercuration and decomposition of di-*tert.*-butylnaphthalic acid produced only one *di-*tert.*-butylnaphthoic acid*, whereas mercuration and decomposition of *tert.*-butylnaphthalic acid had produced a difficultly separable mixture of two *tert.-butylnaphthoic acids*. It was concluded that the di-*tert.*-butylacenaphthene molecule must be symmetrical, and must consequently be 2 : 5-di-*tert.*-butylacenaphthene.

This structure explained the observed *ace*-substitution in the dinitration and the postulated *ace*-substitution in dichlorination and dibromination of the hydrocarbon (see below and in Part II, Peters, *J.*, 1947, 742). The first substituent would enter the 3-position, but as the 4-position is blocked by such bulky groups in the 2-, 3-, and 5-positions, the second substituent would be forced to attack the acenaphthene bridge. *ace*-Substitution cannot be explained by the previously accepted 3 : 4-structure.

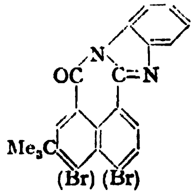
Derivatives of 2-tert.-*Butylacenaphthene and* 2 : 5-*Di*-tert.-*butylacenaphthene*.—Several new derivatives of 2-*tert.*-butylacenaphthene were prepared. From the facts that two *mononitro*-2-tert.-*butylacenaphthenes* were isolated and that *bromo*-2-tert.-*butylacenaphthene* was only obtained in an impure condition even after repeated crystallisation, it can be deduced that in the 2-*tert.*-butylacenaphthene molecule two positions are approximately equally reactive. These are probably the 3 : 4-positions. If, as was done in the case of bromination, the reaction is carried to the di-substituted stage, one product only is obtained in a satisfactory yield and almost immediately in a pure state.

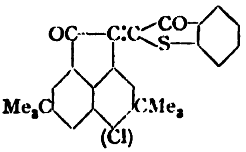
The reaction of *dibromo*-3-tert.-*butylnaphthalic anhydride* with methylamine was of interest, for not only was the compound converted into its *N*-methylimide, but, also, even under mild conditions, one of the bromine atoms was replaced by a methylamino-group. Under similar conditions, ammonia only gave the *imide* and left the bromine atoms unaffected. *o*-Phenylenediamine yielded the yellow *dibromo*-9′-*keto*-2′(or 5′)-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 1)-*benziminazole* (I).

From the general rules of substitution and from those of acenaphthene substitution, it can be assumed that the 3-position of 2 : 5-di-*tert.*-butylacenaphthene is the most reactive. The nomenclature of the many derivatives recorded in Part II must therefore be amended accordingly, the *tert.*-butyl groups being at positions 2 and 5, and the nitro- or bromo-group at 3.

Some further derivatives have now been prepared. Although 2 : 5-di-*tert.*-butylacenaphthene would not react with chlorine in chloroform solution, reaction proceeded smoothly in carbon tetrachloride. 3-*Chloro*-2 : 5-*di*-tert.-*butylacenaphthene* was also prepared, but less satisfactorily, by means of sulphuryl chloride in chloroform solution. The chloro-compound was oxidised, and in addition to the naphthalic anhydride derivative, some quinone was formed, as shown by its ability to condense with 3-hydroxythionaphthen to give the red 3′(or 4′)-*chloro*-2′ : 5′-*di*-tert.-*butyl*-2 : 7′-*thionaphthenacenaphthenylindigo* (II). The 4-*chloro*-3 : 6-*di*-tert.-*butylnaphthalic anhydride* yielded *imides* and also the canary-yellow 3′(or 4′)-*chloro*-9′-*keto*-2′ : 5′-*di*-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′-2 : 1)*benziminazole.*

(I.)





(II.)

The hydrocarbon reacted with 2 mols. of chlorine to give a *dichloro*-2 : 5-*di*-tert.-*butylacenaphthene*. As this compound lost much of its chlorine content upon oxidation, it can be assumed that the second chlorine atom had entered one of the *ace*-positions (cf. dinitro-2 : 5-di-*tert.*-butylacenaphthene; Part II).

2 : 7-*Di*-tert.-*butylnaphthalene*.—Two di-*tert.*-butylnaphthalenes have often been isolated; Gump (*J. Amer. Chem. Soc.*, 1931, **53**, 380) first recognised them as such, but Wegscheider (*Monatsh.*, 1884, **5**, 236) was the first to prepare them. One, m. p. 146—147°, will not form a picrate; the other (recorded m. p.s varying between 80° and 95°) gives a picrate, m. p 157—158°. Tsukervanik and Terentieva (*loc. cit.*) are alone in recording m. p. 132°, picrate, m. p. 99°, for a di-*tert.*-butylnaphthalene.

Contractor, Peters, and Rowe (*J.*, 1949, 1993) obtained the above two hydrocarbons by the action of *tert.*-butyl chloride and aluminium chloride on 2-*tert.*-butylnaphthalene, which had been orientated by Bromby *et al.* (*loc. cit.*), thus showing that one *tert.*-butyl group in each of these hydrocarbons must be in a β-position. They also oxidised the lower-melting isomer by means of potassium permanganate to an acid, the composition of which corresponded to that of a mono-*tert.*-butylphthalonic acid. They therefore concluded that the lower-melting isomer contained the *tert.*-butyl groups in different rings.

Price, Shafer, Huber, and Bernstein (*J. Org. Chem.*, 1942, **7**, 517) decomposed the picrate, m. p. 156—156·5°, to obtain a hydrocarbon, m. p. 80—82°, raised by repeated recrystallisation to 103—104°. A mixture consisting of 2 parts of this recrystallised product, m. p. 103—104°, and 1 part of the di-*tert.*-butylnaphthalene, m. p. 145—146°, melted at 80—82° and was identical with the hydrocarbon, m. p. 80—82°, obtained by decomposition of the picrate, m. p. 156—156·5°. The picrate was thus composed of 2 mols. of di-*tert.*-butylnaphthalene, m. p. 103—104°, 1 mol. of di-*tert.*-butylnaphthalene, m. p. 145—146°, and 2 mols. of picric acid, which constitution was supported by the analyses obtained.

In the present research, a specimen of the picrate, m. p. 157—158°, was analysed, and its constitution agreed with that given by the above authors. It was decomposed, and the hydrocarbon obtained was repeatedly crystallised from alcohol to give colourless, silky needles, m. p. 102—103°. These needles were converted into a *picrate*, an egg-yolk-coloured powder, m. p. 145—146°, not previously prepared. This picrate was dissolved in dry alcohol and the required amount of the di-*tert.*-butylnaphthalene, m. p. 145—146°, dissolved in the same solvent, was added. The mixture was boiled and, on cooling, the orange needles of the picrate, m. p. 157—158°, separated. They gave analyses agreeing with the formula given by Price *et al.* and they showed no depression of m. p. on admixture of the starting material.

Decarboxylation of 3 : 6-di-*tert.*-butylnaphthalic anhydride by soda–lime distillation, by copper-bronze in boiling quinoline, or by mercuration and decomposition, followed by copper-bronze in boiling quinoline, yielded the di-*tert.*-butylnaphthalene, m. p. 102·5—103·5° (picrate, m. p. 145—145·5°). This hydrocarbon is therefore 2 : 7-*di-*tert.*-butylnaphthalene*, which formula satisfies the requirements laid down by Contractor *et al.*

The research is being extended to show whether other Friedel–Crafts alkylations of acenaphthene yield 2-substituted derivatives, whether alkylating agents other than alkyl halide and aluminium chloride yield differently orientated products, and what action aluminium chloride has on alkylacenaphthenes.

EXPERIMENTAL.

(M.p.s are corrected. Micro-analyses were carried out by Drs. Weiler and Strauss, Oxford.)

2-tert.-*Butylacenaphthene.*—A mixture of acenaphthene (308 g., 1 mol.), carbon disulphide (750 c.c.), and aluminium chloride (54 g., 0·2 mol.) was stirred at room temperature and *tert.*-butyl chloride (218 c.c., 1 mol.) was added dropwise during one hour. Stirring was continued at room temperature for 3 hours, and the whole then heated under reflux for 2 hours. After standing overnight, the carbon disulphide solution was poured off and there remained a mixture of granular and tarry complex, which consisted mainly of di-*tert.*-butylacenaphthene and aluminium chloride. The carbon disulphide solution was filtered through charcoal, solvent removed, and the residue distilled at 765 mm. (269 g., 64%). The fractions, b. p. 290—335°, were redistilled at 7 mm., and the part, b. p. 160—174° (66 g., 16%), collected. This was recrystallised twice from acetic acid and then from methyl alcohol, giving colourless plates, m. p. 88—88·5° (Found: C, 91·35; H, 8·6. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%) (Part I; m. p. 73—74° for supposed 3-isomers). The distillation under reduced pressure proved difficult but was indispensable, because fractional distillation at ordinary pressure and fractional crystallisation from a variety of solvents (ethyl alcohol, methyl alcohol, 2-ethoxyethanol, and acetic acid) failed to separate the *tert.*-butylacenaphthene from acenaphthene and di-*tert.*-butylacenaphthene. The difficulty was that the distillates solidified very readily and that the substances involved sublimed easily; the apparatus therefore often became obstructed, yet any rise in pressure caused by such a blockage upset the separation, which can only be controlled by the temperature of distillation.

The above experiment was the best of the many carried out under various conditions. Nitrobenzene, used instead of carbon disulphide, proved unsuccessful as a solvent. On redistillation, the *tert.*-butylacenaphthene distilled at 130—140°/1 mm.

The *picrate* separated in clusters of orange, microcrystalline needles, m. p. 121—123° (Found: C, 60·4; H, 4·8; N, 10·0. $C_{16}H_{18},C_6H_3O_7N_3$ requires C, 60·1; H, 4·8; N, 9·6%). A styphnate could not be prepared.

The 1 : 3 : 5-*trinitrobenzene* complex was obtained as a yellow, microcrystalline powder, m. p. 149—150°, softening at 145° (Found: N, 10·3. $C_{16}H_{18},C_6H_3O_6N_3$ requires N, 9·9%).

Reaction between 3-Bromoacenaphthene and tert.*-Butyl Chloride,* tert.*-Butyl Bromide, or* n*-Butyl Bromide in Presence of Sodium.*—To a solution of 3-bromoacenaphthene (10 g.) and *tert.*-butyl chloride (6 c.c., 1·25 mols.) in sodium-dried ether (50 c.c.) was added finely-divided sodium (1·5 g., 1·5 mols.), and the whole was heated under reflux for 3 hours. From the products, only 3-bromoacenaphthene could be isolated. A similar experiment with *tert.*-butyl bromide also afforded only unchanged bromoacenaphthene.

n-Butyl bromide and 3-bromoacenaphthene reacted spontaneously under conditions similar to the above, and after 2 hours' refluxing only acenaphthene, m. p. and mixed m. p. 93—94°, was isolated (cf. reaction between 3-bromoacenaphthene and *n*-butylmagnesium bromide; Kharasch, Sayles, and Fields, *J. Amer. Chem. Soc.*, 1944, **66**, 481).

3-tert.-*Butylnaphthalic Anhydride.*—This was prepared by oxidation of 2-*tert.*-butylacenaphthene essentially as described in Part I, but on about a double scale; it had m. p. 203—204° (yield 56%), raised by recrystallisation from acetic acid to 204—205°, depressed to below 180° on admixture with 3 : 6-di-*tert.*-butylnaphthalic anhydride, m. p. 211—212°. In Part II, m. p. 201—202° was recorded for the supposed 4-isomer.

N-(2-*Hydroxyethyl*)-3-tert.-*butylnaphthalimide.*—To a solution of 3-*tert.*-butylnaphthalic anhydride in boiling alcohol was added an excess of aqueous ethanolamine. The solution was kept at the boil for

15 minutes and then allowed to cool. Colourless, silky needles separated and were recrystallised from absolute alcohol; m. p. 167—168° (Found: C, 72·7; H, 6·4; N, 4·6. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%).

Oxidation of 3-tert.-*Butylnaphthalic anhydride.*—(*a*) *With potassium permanganate.* Potassium permanganate (10 g.) was added to a solution of 3-*tert.*-butylnaphthalic anhydride (2 g.) in boiling 2·5% aqueous sodium hydroxide (100 c.c.), and the whole left on a steam-bath for 3 days; it was then almost decolorised. A little alcohol was added to destroy any excess of permanganate and the manganese dioxide was filtered off. The filtrate was acidified and extracted with ether. The ether was removed from the extract and the residue was stirred with ligroin; a solid separated which was extracted with ligroin–chloroform and left a white powder, m. p. 207—208° (decomp.; shrinking from 200°) (Found: C, 56·0; H, 4·6. $C_{14}H_{14}O_7$ requires C, 57·15; H, 4·8%). It was impossible to crystallise this acid. Its *trimethyl* ester, prepared by means of diazomethane, after repeated crystallisation from aqueous methyl alcohol, formed beautiful, colourless needles, m. p. 127—129° (Found: C, 60·45, 60·6; H, 6·1, 5·8. $C_{17}H_{20}O_7$ requires C, 60·7; H, 6·0%). The acid is therefore probably 4-tert.-*butyl*-2 : 6-*dicarboxybenzoylformic acid* [cf. Graebe and Bossel, *Annalen*, 1896, **290**, 206; Randall, Benger, and Groocock, *Proc. Roy. Soc.*, 1938, *A*, **165**, 432, who obtained 2 : 6-dicarboxybenzoylformic acid by alkaline permanganate oxidation of naphthalic anhydride and of acenaphthene, acenaphthenequinone, and 3-(*o*-carboxybenzoyl)acenaphthene, respectively].

(*b*) *With nitric acid.* 3-*tert.*-Butylnaphthalic anhydride (0·5 g.), concentrated nitric acid (3 c.c.), and water (2 c.c.) were heated in a sealed tube to 200—220° for 24 hours. The solution was evaporated until solid began to separate and then allowed to cool. The solid was collected, and dried at 100° and then *in vacuo* over phosphoric oxide and sodium hydroxide, to give a white powder, m. p. 249—255° (decomp.), and at 240° as the anhydride (Found: C, 46·3, 46·2; H, 2·2, 2·3. Calc. for $C_{10}H_6O_8$: C, 47·25; H, 2·4%). An aqueous solution of the acid gave, on standing, a white precipitate with barium chloride solution, a reaction not given by benzene-1 : 2 : 3 : 4-tetracarboxylic acid.

The acid (0·25 g.) was covered with ether (10 c.c.), and diazomethane solution (from nitrosomethylurethane, 3 c.c.) was added. Vigorous frothing occurred and after 30 minutes the solid was filtered off; it was an almost colourless nitrogen-containing powder, which shrank a little below 300°, but on further heating it turned yellow and eventually gave off a gas and charred with a little explosion. The filtrate was evaporated to dryness, and the solid crystallised three times from methyl alcohol to give colourless needles, m. p. 106—107°, depressed to 90—93° on admixture of tetramethyl benzene-1 : 2 : 3 : 4-tetracarboxylate (Found: C, 52·9, 53·0; H, 4·5, 4·3. Calc. for $C_{14}H_{14}O_8$: C, 54·2; H, 4·5%).

The product of oxidation with nitric acid was therefore mainly benzene-1 : 2 : 3 : 5-tetracarboxylic acid (cf. Bamford and Simonsen, *J.*, 1910, **97**, 1904; Smith and Byrkit, *J. Amer. Chem. Soc.*, 1933, **55**, 4305). The impurities are probably due to products arising from attack on the nucleus carrying the *tert.*-butyl group.

tert.-*Butyl*-1-*naphthoic Acids* (cf. method of mercuration: Leuck, Perkins, and Whitmore, *J. Amer. Chem. Soc.*, 1929, **51**, 1835; Davies, Heilbron, and Irving, *J.*, 1932, 2715).—Finely-ground 3-*tert.*-butylnaphthalic anhydride (10 g.) was dissolved in water (500 c.c.) containing sodium hydroxide (6·3 g., 4 mols.) by refluxing for some time, a large flask (2 l.) being used in order to avoid frothing over in the later stage. A boiling solution of mercuric oxide (8·6 g., 1 mol.) in a mixture of acetic acid (13 c.c.) and water (37 c.c.) was added, and the slightly red mixture, which was acid to litmus, was refluxed for 98 hours, during which the precipitate became a pure white. It was filtered off, washed, and refluxed with concentrated hydrochloric acid (100 c.c.) and water (200 c.c.) for 2 hours. A lump of solid was formed and this was dissolved in much alcohol. The solution was filtered from a finely-divided white solid, which was insoluble in sodium hydroxide solution and did not melt below 300°. The alcoholic solution was filtered (charcoal) and evaporated to approximately 50 c.c. It was allowed to cool and the precipitate collected. The tert.-*butyl*-1-*naphthoic acid* (1·5 g.) crystallised from alcohol in colourless, irregular crystals, m. p. 167—169° (with previous sintering), unaltered by recrystallisation (Found: C, 79·4; H, 7·2. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·0%).

The residues were evaporated to dryness, yielding a cream-coloured powder, m. p. 110—150° (4·4 g.), which had a distinct odour of 2-*tert.*-butylnaphthalene. Fractional crystallisation from aqueous methyl alcohol, with rejection of the least soluble portions, gave some colourless plates and rods, m. p. 124—127°, of an isomeric tert.-*butyl*-1-*naphthoic acid* (Found: C, 78·9; H, 7·1%).

2-tert.-*Butylnaphthalene.*—(*a*) *From* tert.-*butylnaphthalic anhydride.* 3-*tert.*-Butylnaphthalic anhydride (5 g.) was distilled with soda–lime, giving a small yield of a colourless oil, b. p. 270° (uncorr.), which was converted into a picrate, m. p. 98—99°, not depressed on admixture of authentic 2-*tert.*-butylnaphthalene picrate (Found: C, 57·65; H, 4·7; N, 10·0. Calc. for $C_{14}H_{16},C_6H_3O_7N_3$: C, 58·1; H, 4·6; N, 10·2%). When the experiment was repeated under reduced pressure (*ca.* 20 mm.), a mixture of unchanged anhydride and an oil was obtained. The latter, b. p. 275°, gave 2-*tert.*-butylnaphthalene picrate, m. p. and mixed m. p. 98—99°.

(*b*) *From the* tert.-*butyl*-1-*naphthoic acids.* The crude acids (7 g.) (see above) were boiled with quinoline (20 c.c.) and copper-bronze (2·5 g.) (Sheppard, Winslow, and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2083) and the mixture was distilled with steam after acidification with hydrochloric acid. Ether extraction of the distillate and evaporation of the ether gave a colourless oil (2 g., 39%). The picrate, m. p. 99—100°, prepared from it, showed no depression of m. p. on admixture with authentic 2-*tert.*-butylnaphthalene picrate (Found: C, 58·2; H, 4·6; N, 10·2%).

Bromo-2-tert.-*butylacenaphthene.*—To a solution of 2-*tert.*-butylacenaphthene (5 g.) in cold carbon tetrachloride (50 c.c.) was added slowly and with shaking a solution of bromine (1·3 c.c., 1·1 mols.) in the same solvent (50 c.c.). The mixture was kept with occasional shaking for 1 hour, much hydrogen bromide being evolved. The carbon tetrachloride was gradually replaced by absolute alcohol, and the solution allowed to cool. Tars were obtained and these were crystallised to give three fractions, each of which gave, on repeated crystallisation from alcohol, colourless needles, m. p. 145° (Found: C, 68·2; H, 6·75; Br, 26·05. $C_{16}H_{17}Br$ requires C, 66·4; H, 5·9; Br, 27·7%). The *bromo*-2-tert.-*butylacenaphthene* obtained was therefore impure.

Dibromo-2-tert.-*butylacenaphthene*.—Bromine (1·9 c.c., 2 mols.), dissolved in chloroform (40 c.c.), was added slowly and with shaking to a solution of 2-*tert*.-butylacenaphthene (4 g.) in the same solvent (50 c.c.). The mixture was kept with occasional shaking for 3 hours and then a portion of the chloroform was replaced by absolute alcohol. On cooling, *dibromo*-2-tert.-*butylacenaphthene* (4·2 g., 60%) was deposited and recrystallised from absolute alcohol–chloroform in colourless pillars, m. p. 185—185·5° (Found: C, 52·6; H, 4·5; Br, 43·5. $C_{16}H_{16}Br_2$ requires C, 52·2; H, 4·35; Br, 43·5%). It did not form a picrate in alcoholic solution.

Dibromo-3-tert.-*butylnaphthalic Anhydride*.—To a solution of dibromo-2-*tert*.-butylacenaphthene (2 g.) in boiling acetic acid (100 c.c.), sodium dichromate (8 g.) was added gradually and the solution was heated under reflux for 4 hours, then poured into water; after standing, the colourless precipitate was filtered off and extracted with boiling 5% aqueous sodium carbonate. The extract was acidified, and the resulting solid crystallised from acetic acid containing a little acetic anhydride in colourless, silky needles and plates, m. p. 218—219° (Found: C, 46·95; H, 2·9; Br, 39·5. $C_{16}H_{12}O_3Br_2$ requires C, 46·6; H, 2·9; Br, 38·8%), both forms separating simultaneously; this phenomenon was also noticed with 3 : 6-di-*tert*.-butylnaphthalic anhydride.

Derivatives of Dibromo-3-tert.-*butylnaphthalic Anhydride*.—On being heated under reflux with excess of aqueous ammonia (*d* 0·88), an alcoholic solution of the anhydride gave *dibromo*-3-tert.-*butylnaphthalimide*, which crystallised from absolute alcohol in very pale yellow plates, m. p. 294—295° (Found: N, 3·4; Br, 38·3. $C_{16}H_{13}O_2NBr_2$ requires N, 3·4; Br, 38·9%). On using 33% aqueous methylamine instead of ammonia in a similar reaction, there were obtaind lemon-coloured needles, m. p. 301—302° (Found: N, 6·35; Br, 22·2. $C_{18}H_{19}O_2N_2Br$ requires N, 7·5; Br, 21·3%. $C_{17}H_{15}O_2NBr_2$ requires N, 3·3; Br, 37·6%). In the reaction with methylamine, therefore, not only was the *N*-methylimide formed, but one bromine atom had been replaced to a large extent by a methylamino-group. The anhydride (0·5 g.) and *o*-phenylenediamine (0·15 g.), refluxed in acetic acid for 15 minutes, afforded *dibromo*-9′-*keto*-2′(or 5′)-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′-2 : 1)*benziminazole*, which crystallised from acetic acid in yellow needles, m. p. 250—251° (Found: N, 5·7; Br, 33·4. $C_{22}H_{16}ON_2Br_2$ requires N, 5·8; Br, 33·1%).

Nitro-2-tert.-*butylacenaphthenes*.—To a cold solution of 2-*tert*.-butylacenaphthene (5 g.) in acetic acid (200 c.c.) was added nitric acid (1·65 c.c., 1·1 mols.) dissolved in acetic acid (50 c.c.); the solution, which turned yellow, was kept for 1 hour, then evaporated to small bulk. On cooling, a yellow semicrystalline precipitate separated and this was crystallised three times from absolute alcohol, yielding yellow plates, m. p. 158—159° (0·4 g.) (Found: C, 75·1; H, 6·5; N, 5·7. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%). From the mother-liquor was obtained by repeated crystallisation from alcohol a very small quantity of yellow needles, m. p. 208—210°, with previous softening (Found: N, 5·9%). Two isomeric *nitro*-2-tert.-*butylacenaphthenes* were therefore formed in the nitration of the hydrocarbon.

Nitro-3-tert.-*butylnaphthalic Anhydride*.—Oxidation of the nitro-2-*tert*.-butylacenaphthene, m. p. 158—159° (0·4 g.), with sodium dichromate (2 g.) in boiling acetic acid (30 c.c.) for 3 hours yielded, by the usual procedure, some yellow crystalline masses and plates, m. p. 194—195°, of *nitro*-3-tert.-*butylnaphthalic anhydride* (Found: C, 64·6; H, 4·6; N, 4·6. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·35; N, 4·7%).

2 : 5-*Di*-tert.-*butylacenaphthene* (cf. Part I).—This was prepared essentially as described formerly for the supposed 3 : 4-isomer, but on a four-fold scale; it formed colourless needles, m. p. 162·5—163·5° (Part I, 162—163°). There remained in the flask a fluorescent, orange tar, which on cooling set to a glass, b. p. *ca*. 220°/0·5 mm. (Found: H, 8·3. Calc. for $C_{24}H_{34}$: H, 10·6%). This analysis does not support Buu-Hoï and Cagniant's suggestion (*loc. cit.*) that this consisted of tri-*tert*.-butylacenaphthene. The glass may be of the nature of the yellow-green, fluorescent oil obtained by Niggemann (*Chem. Zentr.*, 1919, II, 584) by boiling acenaphthene with aluminium chloride.

The picrate had m. p. 165—165·5° (Part I, 164°). The 1 : 3 : 5-trinitrobenzene complex was obtained in orange rosettes of needles, m. p. 205—206°, from absolute alcohol (Found: N, 8·75. Calc. for $C_{20}H_{26},C_6H_3O_6N_3$: N, 8·8%).

3 : 6-*Di*-tert.-*butylnaphthalic anhydride* (cf. Part I).—The hydrocarbon was oxidised as before to this anhydride; m. p. 211—212° (211° in Part I for supposed 4 : 5-isomer).

N-(2-*Hydroxyethyl*)-3 : 6-*di*-tert.-*butylnaphthalimide*.—To a solution of the anhydride (1 g.) in boiling alcohol (60 c.c.) was added an excess of aqueous ethanolamine and the whole was heated on the steam-bath for 10 minutes. The *naphthalimide*, which separated on cooling, crystallised from alcohol in silky, colourless needles (0·8 g.), m. p. 248° (Found: C, 75·0; H, 7·6; N, 4·4. $C_{22}H_{27}O_3N$ requires C, 74·8; H, 7·65; N, 4·0%).

Nitric Acid Oxidation of 3 : 6-*Di*-tert.-*butylnaphthalic Anhydride*.—A mixture of the anhydride (0·75 g.), water (2 c.c.), and concentrated nitric acid (4 c.c.) was heated in a sealed tube at 160—180° for 24 hours. Two such experiments yielded a few insoluble pale yellow plates, m. p. up to 170°, which were filtered off. The filtrate was evaporated to dryness, yielding a white powder, which under the microscope appeared as masses of tiny crystals. These melted at 252—254°, shrinking a little before this temperature was reached and giving an opaque liquid which decomposed at 256—257°. On cooling, the liquid solidified immediately and on reheating was clear again by 237°. The powder was extremely soluble in water and an aqueous solution gave, on standing, a white, microcrystalline precipitate with barium chloride solution. The powder was benzene-1 : 2 : 3 : 5-tetracarboxylic acid (Found: C, 47·0; H, 2·4. Calc. for $C_{10}H_6O_8$: C, 47·2; H, 2·4%). The tetramethyl ester was prepared by means of diazomethane in ethereal solution and, after crystallising twice from methyl alcohol, formed rosettes of colourless plates, m. p. 109—110° (Found: C, 53·95; H, 4·3. Calc. for $C_{14}H_{14}O_8$: C, 54·2; H, 4·5%).

In another experiment under the same conditions but with 1·0 g. of anhydride, the solution was not evaporated to dryness, but was allowed to crystallise when it had been reduced to small bulk. Rosettes of needles were obtained and these, crystallised from water, softened at 180°, and melted at 195—198° (Found: C, 54·6; H, 5·6. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%); when dissolved in water they gave an immediate precipitate with barium chloride solution. The analysis approximated to that of a tert.*-butylbenzenetricarboxylic acid*. It can be concluded with certainty that the naphthalene ring had been oxidised before the butyl group was attacked.

*3-Chloro-2 : 5-di-*tert.*-butylacenaphthene.*—To a cold solution of 2 : 5-di-*tert.*-butylacenaphthene (10 g.) in carbon tetrachloride (50 c.c.) was slowly added with frequent shaking during 30 minutes a solution of chlorine (3 g., 1·1 mols.) in the same solvent (50 c.c.); the solution was then kept with occasional shaking for 1 hour. Most, but not all, of the carbon tetrachloride was then evaporated off, and the remainder gradually replaced by absolute alcohol. On cooling, slightly yellow needles (7·8 g., 69%), m p. 118—119°, separated. By repeated crystallisation from absolute alcohol, *3-chloro-2 : 5-di-*tert.*-butylacenaphthene* was obtained as colourless rods, m. p. 124—125° (Found: C, 80·2; H, 8·4; Cl, 12·2. $C_{20}H_{25}Cl$ requires C, 79·9; H, 8·4; Cl, 11·8%). In chloroform solution, or in hot acetic acid, there was no reaction between chlorine and the hydrocarbon.

Alternatively, sulphuryl chloride (3·1 c.c., 1 mol.) was added to a solution of 2 : 5-di-*tert.*-butylacenaphthene (10 g.) in chloroform (50 c.c.); after reaction had subsided, the mixture was heated under reflux for 2 hours, then poured into absolute alcohol, and the whole partly concentrated, then cooled. Impure 3-chloro-2 : 5-di-*tert.*-butylacenaphthene (7 g., 62%) crystallised out in yellow rods, m. p. 118—119°. This product was not as pure as that obtained above; from the most insoluble portion some orange needles, m. p. 299—300° (Found : Cl, 5·4%), were isolated.

*3-Chloro-2 : 5-di-*tert.*-butylacenaphthene picrate* was obtained from alcoholic solution as red needles, m. p. 151—152° (Found: N, 7·9; Cl, 7·4. $C_{20}H_{25}Cl,C_6H_3O_7N_3$ requires N, 7·9; Cl, 6·7%).

*4-Chloro-3 : 6-di-*tert.*-butylnaphthalic Anhydride.*—3-Chloro-2 : 5-di-*tert.*-butylacenaphthene (3·5 g.) was dissolved in boiling acetic acid (150 c.c.), and sodium dichromate (12 g.) added gradually. The whole was refluxed for 2 hours, poured on ice-water, and filtered off after standing. The pale yellow powder (3·3 g., 82%) thus obtained was crystallised once from acetic acid and once from absolute alcohol, yielding colourless, irregular plates of the *anhydride*, m. p. 170·5—171° (Found: C, 69·8; H, 5·8; Cl, 10·9. $C_{20}H_{21}O_3Cl$ requires C, 69·7; H, 6·1; Cl, 10·3%).

The *naphthalimide* crystallised from absolute alcohol in colourless needles, m. p. 294° (Found: C, 70·3; H, 6·8; N, 4·2; Cl, 9·7. $C_{20}H_{22}O_2NCl$ requires C, 69·9; H, 6·4; N, 4·1; Cl, 10·3%). The N*-methylimide* separated from alcoholic solution in colourless needles, m. p. 265° (Found : N, 4·2. $C_{21}H_{24}O_2NCl$ requires N, 3·9%). 3′(or 4′)*-Chloro-9′-keto-2′ : 5′-*tert.*-butyl-8′-azaphenalino*(7′ : 8′ : 2 : 1)*-benziminazole* crystallised from acetic acid in canary-yellow rods, m. p. 270—272° (Found : N, 7·2. $C_{26}H_{25}ON_2Cl$ requires N, 6·7%).

3′(or 4′)*-Chloro-2′ : 5′-di-*tert.*-butyl-2 : 7′-thionaphthenacenaphthenylindigo.*—To a solution of 3-chloro-2 : 5-di-*tert.*-butylacenaphthene (3 g.) in boiling acetic acid (50 c.c.) was added all at once roughly ground sodium dichromate (10 g.), and the mixture was stirred and kept gently boiling for 4 minutes after the reaction had subsided. It was poured on ice-water and filtered. The solid (3 g.) was extracted 6 times with boiling 5% aqueous sodium carbonate (1 l.). Acidification of the combined extracts yielded 4-chloro-3 : 6-di-*tert.*-butylnaphthalic anhydride (1·5 g.). The insoluble, straw-coloured residue, m. p. 135—138° (1·3 g.), was condensed with 2-hydroxythianaphthen by boiling in acetic acid–hydrochloric acid (10 : 1) for 5 minutes to yield a thioindigoid *dye*, which crystallised from acetic acid in bright red needles, m. p. 269—270° (0·4 g.) (Found: Cl, 7·5; S, 7·0. $C_{28}H_{25}O_2ClS$ requires Cl, 7·7; S, 6·95%). This was equivalent to the presence of 0·3 g. of 3-chloro-2 : 5-di-*tert.*-butylacenaphthenequinone, which was thus formed in 9% yield in the above reaction.

3 : 7(or 8)*-Dichloro-2 : 5-di-*tert.*-butylacenaphthene.*—2 : 5-Di-*tert.*-butylacenaphthene (5 g.) was dissolved in carbon tetrachloride (50 c.c.) and, during 30 minutes, a solution of chlorine (2·7 g., 2 mols.) in the same solvent (50 c.c.) was added with shaking. The solution was kept for another 30 minutes, and some of the carbon tetrachloride was then evaporated and the remainder gradually replaced by absolute alcohol. On cooling, there separated an oil, which on repeated crystallisation from absolute alcohol yielded colourless needles, m. p. 139—141° (0·5 g., 8%) (Found: C, 71·5; H, 6·9; Cl, 21·1. $C_{20}H_{24}Cl_2$ requires C, 71·6; H, 7·2; Cl, 21·2%).

Oxidation of the *dichloro*-compound with sodium dichromate in acetic acid solution gave a small quantity of solid, which crystallised from aqueous alcohol in small irregular plates, m. p. 170—172°, not depressed on admixture of authentic 4-chloro-3 : 6-di-*tert.*-butylnaphthalic anhydride (Found : C, 68·9; H, 5·7; Cl, 11·8. Calc. for $C_{20}H_{21}O_3Cl$: C, 69·7; H, 6·1; Cl, 10·3%). These results suggested that the second chlorine atom had entered the di-*tert.*-butylacenaphthene molecule in one of the *ace*-positions.

3 : 6*-Di-*tert.*-butyl-*1*-naphthoic Acid.*—Finely-powdered 3 : 6-di-*tert.*-butylnaphthalic anhydride (13 g.) was boiled with a solution of sodium hydroxide (10 g.) in water (500 c.c.) but only partly dissolved. A hot solution of mercuric oxide (9·1 g.) in a mixture of acetic acid (10 c.c.) and water (30 c.c.) was added. A reddish precipitate formed and the whole was heated under reflux for 80 hours in a 2-l. flask. The precipitate gradually became white; it was filtered off; some globules of mercury had formed. The solid was boiled with dilute hydrochloric acid for 2 hours and filtered off. The insoluble material was dissolved in acetic acid, and the solution filtered from a white substance, m. p. >300°, and allowed to cool. 3 : 6*-Di-*tert.*-butyl-*1*-naphthoic acid* (5 g., 42%) separated, and two recrystallisations from acetic acid, in which it is very soluble, gave small clusters of crystals, m. p. 197—198° (Found: C, 80·3; H, 8·4. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·45%). A second crop (3·7 g., 31%) was obtained and from it crude di-*tert.*-butylnaphthoic acid and crude di-*tert.*-butylnaphthalic anhydride could be isolated.

Derivatives of 3 : 6*-di-*tert.*-butyl-*1*-naphthoic acid.* From absolute alcohol, the *amide* was obtained as colourless, microcrystalline needles, m. p. 212—213° (Found: N, 5·05. $C_{19}H_{25}ON$ requires N, 4·95%), and the p*-toluidide* as colourless, irregular plates, m. p. 221·5—222·5° (Found: N, 3·35. $C_{26}H_{31}ON$ requires N, 3·75%).

2 : 7*-Di-*tert.*-butylnaphthalene.—From* 3 : 6*-di-*tert.*-butylnaphthalic anhydride.* Soda–lime distillation of 3 : 6-di-*tert.*-butylnaphthalic anhydride (5 g.) yielded, on crystallisation from aqueous alcohol, colourless needles, m. p. 102—103° (0·5 g.). Refluxing the anhydride (5 g.) with quinoline (10 c.c.) and copper-bronze (2·5 g.) for 50 minutes and steam-distilling the product from an acid solution gave a substance, m. p. 103—104° (0·3 g.). From the residues was recovered crude anhydride (3·8 g.).

(*c*) Di-(2-carbomethoxyethyl) sulphone (11·9 g.), ethylene glycol (4·2 g., 1·35 mols.), and anhydrous potassium carbonate (0·01 g.) were heated for 2 hours at 180—200°, then for 2 hours at 220—240°/3 mm. and for 6 hours at 250—260°/3 mm. The product was a dark brown solid, m. p. >285°. Poor fibres could be drawn from the melt.

With lithium methoxide as catalyst, pronounced decomposition of the sulphone occurred at the reaction temperature (280—300°), giving a black porous brittle product.

In both cases, but more markedly with the lithium methoxide catalyst, unpleasant-smelling volatile by-products were obtained.

(*d*) Di-(2-carboxyethyl) sulphone (10·5 g.), ethylene diacetate (10·5 g., 1·44 mols.), and toluene-*p*-sulphonic acid (0·05 g.) were heated for 2 hours at 190—210° in nitrogen, and then for 6·5 hours at 230—240°/1—2 mm. An unpleasant-smelling volatile by-product was detected. The product was a black solid, m. p. *ca.* 320—330° (decomp.), with only a poor fibre-forming capacity.

Polyamides.—(*a*) ββ′-Thiodipropionic acid (17·8 g., 0·1 mol.) and hexamethylenediamine (11·6 g., 0·1 mol.) were heated at 190° for 3 hours and then for a further 3 hours at 220°/2 mm. The product was dissolved in *m*-cresol, and the polymer precipitated as a colourless granular powder by pouring the solution into a large volume of ethanol. The dry powder contained 10·8% of nitrogen, as required by a polymer of $(-HN\cdot[CH_2]_6\cdot NH\cdot CO\cdot[CH_2]_2\cdot S\cdot[CH_2]_2\cdot CO-)_n$. The thiopolyamide had an intrinsic viscosity of 1·1 and yielded poor fibres of low tenacity at 217—226°. The polymer was soluble in *m*-cresol and dimethylformamide and had m. p. ~210° (decomp.). The fibres exhibited dichroic properties.

(*b*) The hexamethylenediamine salt of ββ′-thiodipropionic acid (crystals, m. p. 181—182°, from ethyl alcohol) was prepared by mixing equimolar quantities of the acid and the diamine in 50% aqueous alcohol. The salt was heated at 220—230°/1—2 mm. for 3 hours. The polymer was purified by dissolution in *m*-cresol and pouring into a large volume of ethanol. The precipitated thiopolyamide was a colourless substance which yielded fibres of poor strength but having intrinsic viscosity of 1·2. These fibres and those recorded in the previous paragraph can be "cold-drawn" and give highly crystalline *X*-ray diffraction patterns.

An attempt was made to wet spin the thiopolyamides from *m*-cresol solution, using a hypodermic needle and spinning into 10, 20, 25, and 35% aqueous sodium hydroxide (ethanol was unsatisfactory), 25% appearing to be the most useful concentration. No stretch was put on the fibre as spun. The fibres obtained, however, were excessively brittle and disintegrated on the lightest touch.

(*c*) The salt, m. p. 160°, obtained from di-(2-carboxyethyl) sulphone and hexamethylene diamine, was heated in boiling xylenol through which a stream of nitrogen was passed. In the first run, a black sticky resinous material was obtained, and, in the second, a solid which had not melted at 290° but showed appreciable signs of decomposition.

The authors express their thanks to the Directors of Messrs. Courtaulds Ltd. for permission to publish these results and to their colleague, Dr. E. R. Wallsgrove of Coventry, for preparing the polymers from di-(2-carboxyethyl) sulphone.

MESSRS. COURTAULDS LIMITED, TEXTILE RESEARCH LABORATORY,
BOCKING, BRAINTREE, ESSEX

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150. *Deoxy-sugars. Part X. Some Methanesulphonyl and Toluene-*p*-sulphonyl Derivatives of α-Ethyl-2 : 3-dideoxy-*D*-glucoside.*

By S. LALAND, W. G. OVEREND, and M. STACEY.

The methanesulphonyl and toluene-*p*-sulphonyl esters of α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside and α-ethyl-2 : 3-dideoxy-D-glucoside have been prepared and their exchange reactions with sodium iodide in acetone studied. It has been shown that for the former compound, the ethylenic linkage between $C_{(2)}$ and $C_{(3)}$ exerts an activating influence on substituents at $C_{(4)}$.

IT is well known that when 3 : 4 : 6-triacetyl glucal (I) is heated with water it loses an acetyl group and migration of the ethylenic linkage occurs, the product being 4 : 6-diacetyl ψ-glucal (II) (Bergmann, *Annalen*, 1925, **443**, 223). Recently, we used this product as an intermediate in a synthesis of 2-deoxy-D-ribose (Overend and Stacey, *J.*, 1949, 1358) and became interested in the mechanism of this change. The reaction is a fairly general one with acetylated glycals and occurs, not only in the glucose series, but also with galactose (Lohaus and Widmaier, *Annalen*, 1935, **520**, 301) and arabinose derivatives (Gehrke and Aichner, *Ber.*, 1927, **60**, 918).

When D-glucal was boiled with water, under conditions similar to those used for preparing diacetyl ψ-glucal from triacetyl glucal there was no migration of the double bond and the initial material was recovered unchanged. In a like manner when D-glucal was heated with water containing acetate ions it underwent no change. However, when glucal was heated under like conditions with acetic acid a reaction did occur and some of the glucal (20%) was converted into 2-deoxy-D-glucose which was isolated from the syrupy reaction product as its dibenzyl mercaptal (Overend, Stacey, and Staněk, *J.*, 1949, 2841). However the main product, which was very labile, was not isolated in crystalline form. From these preliminary experiments it appeared

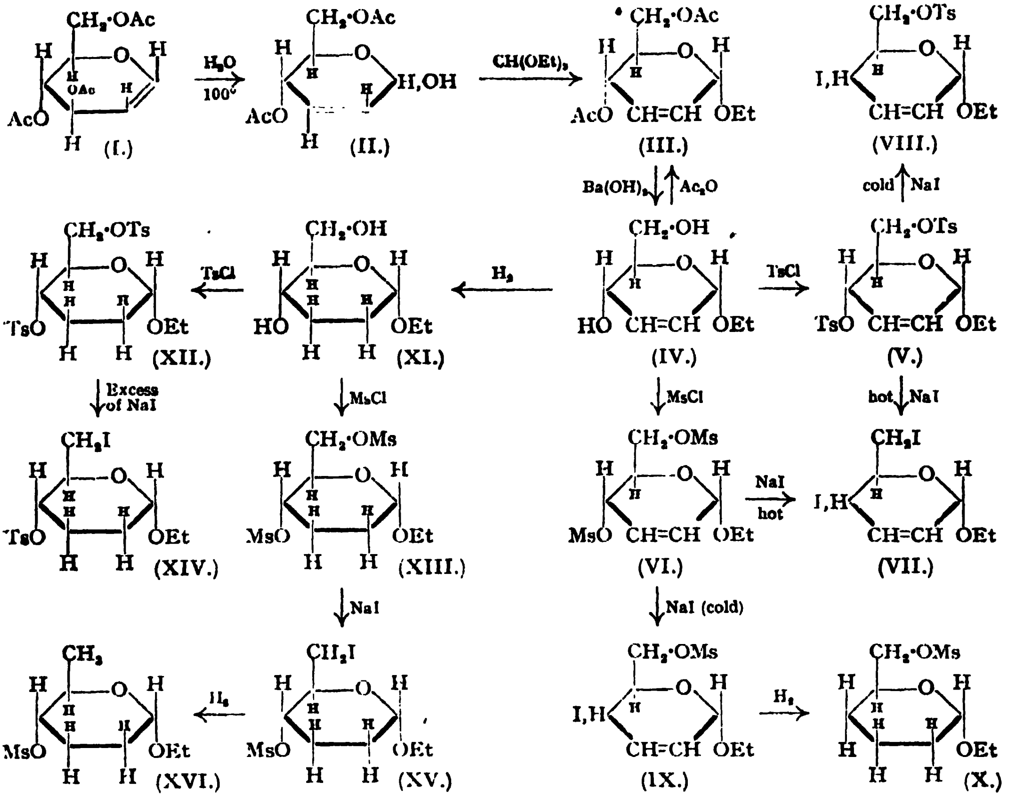
that the ethylenic linkage between $C_{(1)}$ and $C_{(2)}$ in triacetyl glucal activated the acetyl substituent at $C_{(3)}$ so that gentle heating with water was sufficient to eliminate it, and the acidity consequently developed induced migration of the double bond. Recently, whilst working with methanesulphonyl and toluene-*p*-sulphonyl esters we have obtained some evidence of the activating influence of ethylenic linkages on substituents in molecules of this type.

Generally, when a primary hydroxyl group is esterified with a toluene-*p*-sulphonyl or methanesulphonyl residue, the toluene-*p*-sulphonyloxy- or methanesulphonyloxy-group can be exchanged for iodine by the simple expedient of heating with sodium iodide in acetone or in a higher-boiling ketone. When a secondary hydroxyl group in a sugar derivative is similarly esterified, the residues are with a few exceptions not usually replaced. Helferich and Gnüchtel (*Ber.*, 1938, **71**, 712; see also Helferich and Jochinke, *Ber.*, 1940, **73**, 1049) did, however, convert 1 : 2 : 3 : 6-tetra-acetyl 4-methanesulphonyl D-glucose into its corresponding 4-iodo-4-deoxy-derivative by the usual procedure, and a further exception to the general rule was encountered when adjacent primary and secondary hydroxyl groups were esterified with toluene-*p*-sulphonyl residues, since treatment of these esters with sodium iodide in acetone resulted in the elimination of both toluene-*p*-sulphonyloxy-groups and formation of an unsaturated compound (Hahn, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73). The toluene-*p*-sulphonyloxy-residues in the open-chain compounds *iso*mannide and *iso*sorbide (cf. Montgomery and Wiggins, *J.*, 1946, 393) are also exchanged although they are formed by esterification of secondary hydroxyl groups. In these compounds, however, the anhydro-rings may exert some influence. In this communication we describe further instances in unsaturated derivatives of sugars, of the exchange for iodine of methanesulphonyloxy- and toluene-*p*-sulphonyloxy-residues formed by appropriate esterification of secondary hydroxyl groups.

3 : 4 : 6-Triacetyl D-glucal (I) was heated with water and converted into 4 : 6-diacetyl 2 : 3-didehydro-2 : 3-dideoxy-D-glucose (diacetyl *ψ*-glucal) (II), which was immediately treated with ethyl orthoformate in ethanol to yield 4 : 6-diacetyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (III) previously described by Bergmann (*Annalen*, 1925, **443**, 223). Deacetylation of this with barium hydroxide yielded α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (IV) (Bergmann and Freudenberg, *Ber.*, 1931, **64**, 158). That no other change accompanied this deacetylation was apparent from the fact that (IV) could be acetylated smoothly with acetic anhydride to re-form (III). Moreover, (IV) was non-reducing to lead tetra-acetate in benzene solution, showing that it retained its pyranose structure. It formed a crystalline 4 : *6-di*-p-*nitrobenzoate* which was a suitable derivative for characterisation. Treatment with toluene-*p*-sulphonyl chloride in dry pyridine afforded crystalline 4 : *6-ditoluene*-p-*sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy*-D-*glucoside* (V); similarly with methanesulphonyl chloride a crystalline 4 : *6-dimethanesulphonyl* derivative (VI) was obtained. When either the ditoluene-*p*-sulphonyl (V) or the dimethanesulphonyl derivative (VI) was heated with excess of sodium iodide in acetone at 110—115° for 3 hours, there was obtained crystalline 4 : *6-di-iodo α-ethyl-2 : 3-dehydro-2 : 3 : 4 : 6-tetradeoxy*-D-*hexoside* (VII). When, however, the toluene-*p*-sulphonyl derivative (V) was kept for 3 days at 30° with 1·1 moles of sodium iodide in acetone, it gave a monoiodo monotoluene-*p*-sulphonyl derivative (VIII). By analogy with subsequent work this was probably *4-iodo 6-toluene*-p-*sulphonyl α-ethyl-2 : 3-didehyrod-2 : 3 : 4-trideoxy*-D-*hexoside*, but, since it was unstable to the reduction process needed to establish its structure, we concentrated our attention on the corresponding methanesulphonyl derivative which was more stable to this treatment.

When 4 : 6-dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (VI) was kept at 18° for 5 days in the dark with sodium iodide in acetone it yielded 1 mole of sodium methanesulphonate together with a very unstable monoiodo monomethanesulphonyl α-ethyl-hexoside (IX). This rapidly liberated iodine when exposed to light or mild warming and so was immediately hydrogenated. A monomethanesulphonyl α-ethyl-trideoxy-hexoside was obtained. This could be either *6-methanesulphonyl α-ethyl-2 : 3 : 4-trideoxy*-D-*glucoside* (X) or 4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside according to whether the methanesulphonyloxy-groups undergoing exchange had been formed by the esterification of a secondary or a primary hydroxyl group respectively. That it was, in fact, the former compound, was demonstrated by synthesising, by an alternative route, the 4-methanesulphonyl derivative, which proved to be different from (X).

Bergmann (*Annalen*, 1925, **443**, 236) showed that when α-ethyl 2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (IV) was reduced it yielded α-ethyl-2 : 3-dideoxy-D-glucoside (XI). This afforded crystalline 4 : *6-ditoluene*-p-*sulphonyl* and 4 : *6-dimethanesulphonyl* derivatives (XII and XIII). When (XII) was heated at 110° for 6 hours with excess of sodium iodide in acetone it gave crystalline *6-iodo 4-toluene-*p*-sulphonyl α-ethyl-2 : 3 : 6-trideoxy-*D*-glucoside* (XIV). Similarly, when 4 : 6-dimethanesulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside (XIII) and sodium iodide in



(Ts = Toluene-*p*-sulphonyl. Ms = Methanesulphonyl.)

acetone were heated at 110—120° for 6 hours, one mole of sodium methanesulphonate was precipitated and syrupy 6-iodo 4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside (XV) was formed. That these compounds were correctly designated was shown by the fact that further heating with excess of sodium iodide did not result in more exchange; moreover, the conditions employed for the exchange reactions were those designed to effect reaction between sodium iodide and toluene-*p*-sulphonyloxy- or methanesulphonyloxy-residues formed by appropriate esterification of a primary hydroxyl group (see also Overend and Stacey, *J.*, 1949, 1235; Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542). 6-Iodo 4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside (XV) darkened on being kept for a short time, so it was reduced immediately on isolation by shaking it in an atmosphere of hydrogen with Raney nickel and diethylamine (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1946, 68, 628). The treatment yielded *4-methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-*D*-glucoside* (XVI), which failed to react when heated at 115—120° for 5½ hours with sodium iodide in acetone, thereby indicating that the methanesulphonyl substituent was attached to a secondary hydroxyl group (Overend, Stacey, *et al.*, *loc. cit.*). On the other hand, the compound (X), provisionally designated as 6-methanesulphonyl α-ethyl-2 : 3 : 4-trideoxy-D-glucoside, afforded sodium methanesulphonate (53%; cf. Foster, Overend, Stacey, and Wiggins, *loc. cit.*) when subjected to the same treatment. This result indicated that the methanesulphonyl residue remaining in the compound (X) was attached at $C_{(6)}$ of the sugar.

The interesting fact emerges from this work that, contrary to expectation, when 4 : 6-dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (VI) is kept with sodium iodide in acetone, the methanesulphonyloxy-group formed by exterification of the secondary hydroxyl group exchanges for iodine before that formed by esterification of the primary hydroxyl group. Similar results are obtained with the toluene-*p*-sulphonyl esters of α-ethyl-2 : 3-di-

dehydro-2 : 3-dideoxy-D-glucoside. The ethylenic linkage between $C_{(2)}$ and $C_{(3)}$ clearly confers lability on the substituent on the hydroxyl group of the adjacent carbon atom 4. This is analogous to the elimination of an acetyl group when triacetyl glucal is boiled with water. In this case the acetyl group eliminated is that at $C_{(3)}$ which has an adjacent ethylenic linkage between $C_{(1)}$ and $C_{(2)}$.

EXPERIMENTAL.

4 : 6-*Diacetyl α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside.*—3 : 4 : 6-Triacetyl D-glucal (10 g.) and water (200 c.c.) were heated under reflux for 15 minutes. Water was then removed at 40°, and the residue was dried by distilling ethanol over it. A yellow syrup remained which strongly reduced Fehling's solution. This was heated under reflux with ethyl orthoformate (6·4 g.) and absolute ethanol (10 c.c.) for 50 minutes. Ammonium chloride (50 mg.) was added during the reaction. The ethanol and excess of ethyl orthoformate were removed by evaporation *in vacuo*, and the residue crystallised. It recrystallised from 96% ethanol as colourless needles (2·0 g.), m. p. 78—79°, $[\alpha]_D^{17}$ +106·7° (*c*, 2·1 in benzene). Bergmann (*Annalen*, 1925, **443**, 223) reports m. p. 81—82° and $[\alpha]_D^{20}$ +102·7° in benzene for this compound.

α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside.—4 : 6-Diacetyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (1·4 g.) was kept with barium hydroxide (3·58 g.) in water (35 c.c.) for 24 hours at room temperature. The excess of barium hydroxide was neutralised with carbon dioxide, and the solution centrifuged. The filtrate was evaporated, and the residue extracted with ethanol (3 × 100 c.c.). Solvent was removed from the extract, and the residue was recrystallised from benzene, forming colourless needles (0·64 g.), m. p. 90—93° (unchanged after repeated recrystallisation). After recrystallisation from ethyl acetate, the m. p. was 94—97°. Sublimation of the material (70°/15 mm.) afforded needles, m. p. 96—97°, $[\alpha]_D^{20}$ +99·5° (*c*, 0·54 in ethanol) (Found : C, 54·95; H, 8·0. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·0%). Bergmann and Freudenberg (*Ber.*, 1931, **64**, 158) give m. p. 100—101°, $[\alpha]_D^{20}$ 100·3° in ethanol for this compound. It was not oxidised by lead tetra-acetate in benzene but could be reacetylated with acetic anhydride to yield 4 : 6-diacetyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside in 80% yield.

4 : 6-*Di*-p-*nitrobenzoyl α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside.*—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (50 mg.) was dissolved in dry pyridine (0·5 c.c.), and *p*-nitrobenzoyl chloride (130 mg., 2·12 mols.) was added. After 18 hours at room temperature, the solution was poured into water (25 c.c.). The solid which separated was recrystallised from 96% ethanol, and 4 : 6-*di*-p-*nitrobenzoyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside* was obtained as colourless needles (100 mg.), m. p. 129—130°, $[\alpha]_D^{19}$ +109·5° (*c*, 0·66 in benzene) (Found : C, 55·7; H, 4·5; N, 6·1. $C_{22}H_{20}O_{10}N_2$ requires C, 55·9; H, 4·3; N, 5·9%).

4 : 6-*Ditoluene*-p-*sulphonyl α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside.*—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·75 g.) was kept at room temperature for 18 hours with toluene-*p*-sulphonyl chloride (0·7 g.) in dry pyridine (0·5 c.c.). The mixture was poured into water, and the precipitated solid filtered off. Recrystallisation from 90% ethanol afforded the *ditoluene*-p-*sulphonyl* derivative (0·12 g.) as colourless needles, m. p. 119—120°, $[\alpha]_D^{15}$ +59° (*c*, 2·16 in benzene) (Found : C, 54·5; H, 5·5; S, 13·0. $C_{22}H_{26}O_8S_2$ requires C, 54·7; H, 5·4; S, 13·2%).

4 : 6-*Dimethanesulphonyl α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside.*—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·75 g.), methanesulphonyl chloride (1·15 g., 0·78 c.c.), and dry pyridine (0·5 c.c.) were kept together at 0° for 75 hours. The mixture was worked up in the usual manner, and after recrystallisation from 85% ethanol 4 : 6-*dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside* (0·72 g.) was obtained as colourless needles, m. p. 71—72°, $[\alpha]_D^{20}$ +87·7° (*c*, 1·46 in acetone) (Found : C, 36·4; H, 5·9. $C_{10}H_{18}O_8S_2$ requires C, 36·4; H, 5·5%).

α-Ethyl-2 : 3-dideoxy-D-glucoside.—α-Ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·4 g.), dissolved in dry methanol (20 c.c.), was hydrogenated at room temperature in the presence of platinic oxide (100 mg.). The solution was filtered, and the methanol evaporated. The residue crystallised from benzene–light petroleum as colourless needles (0·35 g., 83%), m. p. 67—69° $[\alpha]_D^{20}$ +140·6° (*c*, 0·69 in water) (Found : C, 54·4; H, 8·99. Calc. for $C_8H_{16}O_4$: C, 54·5; H, 9·1%). Bergmann (*loc. cit.*) reports m. p. 72—72·5°, $[\alpha]_D^{20}$ +137·8° in water for this compound.

4 : 6-*Ditoluene*-p-*sulphonyl α-Ethyl-2 : 3-dideoxy-D-glucoside.*—α-Ethyl-2 : 3-dideoxy-D-glucoside (0·25 g.), toluene-*p*-sulphonyl chloride (0·66 g.), and dry pyridine (1·5 c.c.) were kept at room temperature for 60 hours. The mixture was poured into water, and the product isolated in the usual manner. After recrystallisation from ethanol 4 : 6-*ditoluene*-p-*sulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside* (0·5 g.) was obtained as colourless needles, m. p. 58—60°, $[\alpha]_D^{20}$ +85° (*c*, 0·89 in benzene) (Found : C, 54·6; H, 5·9. $C_{22}H_{28}O_8S_2$ requires C, 54·5; H, 5·8%).

4 : 6-*Dimethanesulphonyl α-Ethyl-2 : 3-dideoxy-D-glucoside.*—α-Ethyl-2 : 3-dideoxy-D-glucoside (0·3 g.), methanesulphonyl chloride (0·32 c.c.), and dry pyridine (0·5 c.c.) were kept at 0° for 12 hours. The mixture was then poured into water, and the oil which separated was extracted with chloroform. The extract was washed with dilute sulphuric acid (2%) and then water, and dried ($MgSO_4$). Evaporation of the solvent yielded a syrup which crystallised when triturated with water. Recrystallisation of the solid from 90% ethanol yielded the *dimethanesulphonyl* derivative (0·14 g.) as colourless needles, m. p. 68—69°, $[\alpha]_D^{20}$ +118·7° (*c*, 1·11 in acetone) (Found : C, 36·4; H, 5·8. $C_{10}H_{20}O_8S_2$ requires C, 36·2; H, 6·0%).

6-*Iodo 4-Toluene*-p-*sulphonyl α-Ethyl-2 : 3 : 6-trideoxy-D-glucoside.*—4 : 6-Ditoluene-*p*-sulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside (0·3 g.), sodium iodide (0·252 g.), and dry acetone (12 c.c.) were heated in a sealed tube at 110° for 6 hours. Sodium toluene-*p*-sulphonate was precipitated. This was collected by filtration, washed with anhydrous acetone, dried, and weighed (0·130 g. = 100% replacement of one toluene-*p*-sulphonyl group). The acetone solution was evaporated, and the residue treated with chloroform and water. The chloroform layer was washed with dilute sodium thiosulphate solution, dried ($MgSO_4$), and evaporated. The residue slowly crystallised and was recrystallised from 80% ethanol. 6-*Iodo 4-toluene*-p-*sulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside* (0·2 g.) was obtained as colourless needles, m. p. 58—59°, $[\alpha]_D^{17}$ +88·8° (*c*, 0·39 in benzene) (Found: C, 40·3; H, 5·2; I, 29·1. $C_{15}H_{21}O_5SI$ requires C, 40·8; H, 4·9; I, 28·8%).

4 : 6-*Di-iodo* α-*Ethyl*-2 : 3-*dehydro*-2 : 3 : 4 : 6-*tetradeoxy*-D-*hexoside*.—(*a*) 4 : 6-Ditoluene-*p*-sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·72 g.) and dry sodium iodide (0·6 g.) in dry acetone (17 c.c.) were heated together at 110—115° for 3 hours. (Milder exchange conditions yielded only syrupy products.) The amount of sodium toluene-*p*-sulphonate formed (0·55 g.), after filtration, washing with acetone and drying, corresponded to 93% replacement of both toluene-*p*-sulphonyl residues. The acetone was evaporated, and the residue extracted with chloroform (50 c.c.). The extract was washed with dilute sodium thiosulphate solution and dried ($MgSO_4$). After evaporation of the chloroform, the residue partly crystallised. This was recrystallised from 80% ethanol and 4 : 6-*di-iodo* α-*ethyl*-2 : 3-*dehydro*-2 : 3 : 4 : 6-*tetradeoxy*-D-*hexoside* (0·12 g.) was obtained as colourless needles, m. p. 97—98°, $[\alpha]_D^{15}$ −364·8° (*c*, 1·88 in chloroform) (Found: C, 24·6; H, 3·1; I, 63·1. $C_8H_{12}O_2I_2$ requires C, 24·3; H, 3·0; I, 63·5%). This compound was very unstable, and iodine was liberated even after 1 day in the dark. Decomposition was complete in 10 days.

(*b*) 4 : 6-Dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·3 g.), sodium iodide (0·3 g.), and dry acetone were heated at 105—110° for 3 hours. The sodium methanesulphonate formed corresponded to 93% replacement of both methanesulphonyl groups. The product was isolated as above but showed no tendency to crystallise. It was dissolved in benzene (10 c.c.) and run through a short column of alumina, which was then washed with benzene (20 c.c.); 5 c.c. portions (*a*, *b*, *c*, and *d*) were collected; (*a*), (*c*), and (*d*) when evaporated gave syrupy products, but (*b*) yielded crystals which recrystallised from 80% ethanol (0·0279 g.) as colourless needles, m. p. 97—98° alone or in admixture with the di-iodo-compound described above.

4-*Iodo* 6-*Toluene*-p-*sulphonyl* α-*Ethyl*-2 : 3-*didehydro*-2 : 3 : 4-*trideoxy*-D-*hexoside*.—4 : 6-Ditoluene-*p*-sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·5 g.), dry acetone (15 c.c.), and dry sodium iodide (0·175 g. = 1·1 mols.) were kept in a stoppered flask, protected from light, at 18° for 9 days. The reaction mixture became yellow owing to liberated iodine, and sodium toluene-*p*-sulphonate (0·15 g. = 75% replacement of one toluene-*p*-sulphonyloxy-group) was precipitated (Found: C, 43·3; H, 3·6. Calc. for $C_7H_7O_3SNa$: C, 43·4; H, 3·6%).

After separation of this salt, the acetone was evaporated, and the residue extracted with chloroform. After being washed with 1% sodium thiosulphate, the extract was dried ($MgSO_4$) and the solvent evaporated. The only crystalline material which could be isolated from the residue was unchanged 4 : 6-ditoluene-*p*-sulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·04 g.), m. p. 119—120°. If the temperature at which the exchange was carried out was raised to 25°, then sodium toluene-*p*-sulphonate equivalent to 83% replacement was obtained. At 30°, however, complete replacement was effected. The unsaturated ditoluene-*p*-sulphonyl derivative (0·2 g.), sodium iodide (0·061 g.), and dry acetone (5·5 c.c.) were kept together in a stoppered flask protected from light at 30° for 3 days. The product was isolated in the usual manner and a syrup was obtained (0·146 g.). This was purified by passage through a column of alumina, and a straw-coloured syrup (0·096 g.) was obtained: $[\alpha]_D^{20}$ −59·6° (*c*, 1·5 in benzene) (Found: C, 40·9; H, 4·4; OEt, 9·96. $C_{15}H_{19}O_5SI$ requires C, 41·1; H, 4·3; OEt, 10·28%). This syrupy *compound* was unstable and on storage liberated much iodine in 2 days. Attempts to hydrogenate the ethylenic linkage resulted in the uptake of more than 1 mol. of hydrogen even at room temperature.

6-*Methanesulphonyl* α-*Ethyl*-2 : 3 : 4-*trideoxy*-D-*glucoside*.—4 : 6-Dimethanesulphonyl α-ethyl-2 : 3-didehydro-2 : 3-dideoxy-D-glucoside (0·595 g.), sodium iodide (0·29 g. = 1·2 mols.), and dry acetone (10 c.c.) were kept together at 18° for 5 days in absence of light. Sodium methanesulphonate (0·19 g.) separated and was removed by filtration. The product was isolated in the usual manner (0·60 g.) and purified by passage through a column of alumina. A syrup was obtained which was very unstable and sensitive to light and mild heating. It readily liberated iodine and so, as soon as it was isolated, it was hydrogenated in methanol (15 c.c.) containing diethylamine (0·36 c.c.) and a trace of water. Raney nickel was used as catalyst and the mixture was shaken at room temperature for 3·5 hours in an atmosphere of hydrogen at 20 mm. over-pressure. The solution was filtered, and the solvent evaporated. The residue was treated with chloroform and water. The aqueous layer gave a strong positive test for iodide ions. The chloroform layer was dried ($MgSO_4$), and the solvent evaporated. A pale yellow syrup remained (0·33 g.) which gave a positive test for sulphur and a negative test for iodine and had $[\alpha]_D^{20}$ +65·3° (*c*, 2·45 in acetone). It was 6-*methanesulphonyl* α-*ethyl*-2 : 3 : 4-*trideoxy*-D-*glucoside* (Found: C, 45·4; H, 7·3; S, 12·8. $C_9H_{18}O_5S$ requires C, 45·4; H, 7·5; S, 13·4%).

4-*Methanesulphonyl* α-*Ethyl*-2 : 3 : 6-*trideoxy*-D-*glucoside*.—4 : 6-Dimethanesulphonyl α-ethyl-2 : 3-dideoxy-D-glucoside (0·13 g.) and sodium iodide in dry acetone (0·07 g. in 10 c.c.) were heated at 115—120° for 6 hours. Separation of sodium methanesulphonate (0·044 g. = 95·6% replacement of 1 methanesulphonyloxy-group) commenced immediately, and replacement seemed easier to effect than with toluene-*p*-sulphonyl esters. The solid was filtered off, and the filtrate was evaporated to dryness. Water and chloroform were added to the residue, and the chloroform layer was separated, washed (dilute sodium thiosulphate solution), and dried ($MgSO_4$). Evaporation of the solvent afforded some syrup, which was dissolved in methanol (10 c.c.) containing diethylamine (0·1c.c.) and shaken with Raney nickel in an atmosphere of hydrogen at a slight over-pressure. When the uptake of hydrogen ceased, the solution was filtered and evaporated. The residue was treated with water and chloroform. The aqueous layer gave a strong positive test for iodide ions. The chloroform layer was dried ($MgSO_4$), and the solvent evaporated. A yellow syrup (0·087 g.) remained which was free from iodine. It was 4-*methanesulphonyl* α-*ethyl*-2 : 3 : 6-*trideoxy*-D-*glucoside*, $[\alpha]_D^{20}$ +122·9° (*c*, 2·17 in acetone) (Found: C, 46·1; H, 7·5; OEt, 18·7. $C_9H_{18}O_5S$ requires C, 45·4; H, 7·5; OEt, 18·9%).

Exchange Experiments.—(*a*) 4-Methanesulphonyl α-ethyl-2 : 3 : 6-trideoxy-D-glucoside (0·063 g.) was heated with sodium iodide (0·063 g.) in dry acetone (7·0 c.c.) at 115—120° for 5½ hours. No sodium methanesulphonate was formed and the initial materials could be recovered. (*b*) 6-Methanesulphonyl α-ethyl-2 : 3 : 4-trideoxy-D-glucoside (0·178 g.) and sodium iodide (0·12 g.) in acetone (9 c.c.) were heated together under identical conditions. Sodium methanesulphonate (0·047 g.) was precipitated and was collected, washed with dry acetone, dried, and weighed. It corresponded to 53% replacement of the methanesulphonyloxy-residue in the initial material.

Experiments with Glucal.—(*a*) Glucal (1 g.) was boiled with water (12 c.c.) for 15 minutes. There was no change in optical rotation ($[\alpha]_D$ −7·5°) and the D-glucal could be recovered unchanged. (*b*) Glucal (0·5 g.) was dissolved in water (6 c.c.) containing crystalline sodium acetate (0·5 g.), and the solution boiled for 30 minutes. There was no change in optical rotation, and the solution developed no reducing power to Fehling's solution. (*c*) Glucal (1·08 g.) was dissolved in water (40 c.c.) containing acetic acid (0·040 g.), and the solution boiled. The change in optical rotation was followed polarimetrically:

Time (mins.)	0	20	40	60	80
$[\alpha]_D^{20}$	−7·8°	+3·9°	+10·4°	+16·6°	+16·6°

The solution soon rapidly restored the colour to Schiff's reagent. After neutralisation and evaporation, toluene-ω-thiol was added to the syrup together with concentrated hydrochloric acid. The product was isolated as described by Overend, Stacey, and Staněk (*J.*, 1949, 2841) and 2-deoxy-D-glucose dibenzyl mercaptal (20%), m. p. 147—148°, was obtained but no derivative of 2 : 3-didehydro-2 : 3-deoxy-D-glucose.

Certain of the analyses were carried out by Drs. Weiler and Strauss (Oxford). Our thanks are due to the British Empire Cancer Campaign (Birmingham Branch) for financial assistance. One of us (S. L.) thanks the University of Oslo for the award of a Familien Stillesen's grant which enabled him to take part in this work.

Chemistry Department,
The University, Birmingham, 15.

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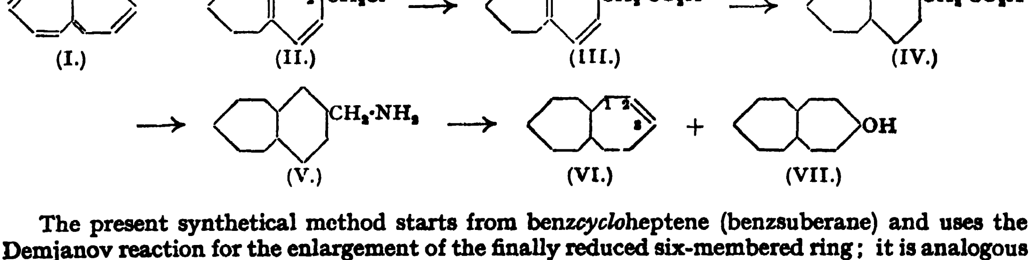
151. *Attempts to Prepare New Aromatic Systems. Part II. Heptalene.*

By G. O. Aspinall and Wilson Baker.

Experiments were directed towards the synthesis of heptalene (I). Benz*cyclo*heptene is converted through its 2′-chloromethyl derivative (II) into the fully saturated aminomethyl compound (V), which yields by the Demjanov reaction a 3-hydroxydodecahydroheptalene and a decahydroheptalene (VI). Attempts to effect catalytic dehydrogenation of (VI) have been unsuccessful.

In model experiments leading to the hydroazulene series ethyl δ-2-keto*cyclo*pentylvalerate (VIII) has been converted into the ketones (XI) and (XII).

The possibility that a bicyclic, unsaturated hydrocarbon of aromatic type possessing two fused seven-membered rings might be prepared was first mentioned by Baker (*J.*, 1945, 264). This substance (I), for which the name heptalene has been used by one of us on numerous occasions since 1944, is a ring homologue of azulene, and the present experiments were begun with the object of attempting to prepare this hydrocarbon. Partly because collaboration between the authors is no longer possible, and partly because others have started work in this series (Horn and Rapson, *Nature*, 1947, **160**, 829; *J.*, 1949, 2421; see also Büchi and Jeger, *Helv. Chim. Acta*, 1949, **32**, 538, who have described the synthesis of certain derivatives of 5 : 5 : 0-*bicyclo*dodecane), it is thought desirable to publish our experiments so far as they have progressed. There is as yet no factual information as to the existence or non-existence of compounds of the "aromatic" heptalene type, although some calculations have been made in the attempt to assess the probable stability of such a conjugated system (Craig and Maccoll, *Nature*, 1948, **161**, 481; *J.*, 1949, 964).

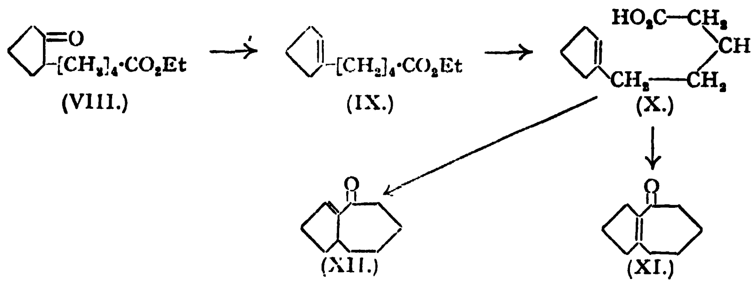


The present synthetical method starts from benz*cyclo*heptene (benzsuberane) and uses the Demjanov reaction for the enlargement of the finally reduced six-membered ring; it is analogous to a synthesis of azulene from indane described by Arnold (*Ber.*, 1943, **76**, 777; cf. also Plattner, Fürst, and Studer, *Helv. Chim. Acta*, 1947, **30**, 1091). Chloromethylation of benz*cyclo*heptene yielded *2′-chloromethylbenz*cyclo*heptene* (II) which is orientated by analogy, and this was then converted into, successively, *2′-cyanomethylbenz*cyclo*heptene* and the homogeneous, crystalline *benz*cyclo*heptene-2′-acetic acid* (III). The *ethyl* ester of (III) was reduced with hydrogen in presence of Adams's platinum oxide catalyst to *ethyl* cyclo*hexano*cyclo*heptane-2′-acetate*, hydrolysis of which yielded an almost homogeneous cyclo*hexano*cyclo*heptane-2′-acetic acid* (IV). Application of the von Auwers–Skita rule (von Auwers, *Annalen*, 1920, **420**, 84; Skita, *Ber.*, 1920, **53**, 1792) suggests that the acid (IV) probably possesses the *cis*-configuration of the two rings. Treatment of this acid with sodium azide under the conditions of the Schmidt reaction then gave *2′-aminomethyl*cyclo*hexano*cyclo*heptane* (V), characterised as the crystalline *benzoyl* derivative. The action of nitrous acid on (V) yielded an unsaturated hydrocarbon, probably the *Δ^{1}-decahydroheptalene* (VI), and an alcohol, probably 3-hydroxydodecahydroheptalene (VII), which was not obtained pure.

A few attempts have been made to dehydrogenate decahydroheptalene (VI) over palladium-charcoal at 310—330°/14 mm.; the product, a colourless oil, possessed a higher refractive index than (VI) and was unsaturated, but did not yield a picrate. The lengthy synthetical processes involved in the preparation of the aminomethyl compound (V) have allowed the final reactions which might lead to the synthesis of heptalene to be performed only on a very small scale.

A second projected synthesis of heptalene involved the formation of a seven-membered ring by the cyclodehydration of a suitable unsaturated acid, as in (X). This method has now, however, been described by Büchi and Jeger (*loc. cit.*), who started from a *cyclo*heptane derivative, but our preliminary experiments to test the feasibility of this approach started from a *cyclo*pentane and led to the reduced azulene series.

Ethyl *cyclo*pentanone-2-carboxylate was condensed with ethyl δ-iodovalerate giving *ethyl δ-(2-keto-1-carbethoxy*cyclo*pentyl)valerate*, which was simultaneously hydrolysed and decarboxylated, and then esterified, yielding *ethyl δ-2-keto*cyclo*pentylvalerate* (VIII). The ketone (VIII) was then reduced by the Meerwein–Ponndorf method to the secondary alcohol, and dehydrated with thionyl chloride to the unsaturated ester, probably mainly *ethyl δ-cyclopent-1-enylvalerate* (IX). Hydrolysis of (IX) yielded the corresponding acid (X) (uncharacterised), which was cyclised (*a*) by treatment of the acid chloride with stannic chloride in carbon disulphide (method due to Cook and Lawrence, *J.*, 1935, 1037), and (*b*) by treatment of the free acid with zinc chloride in acetic acid–acetic anhydride (method due to Bachmann and Dreiding, *J. Org. Chem.*, 1948, **13**, 324). Both cyclisation procedures yielded small quantities of liquid ketonic products giving deep-red *2 : 4-dinitrophenylhydrazones*, $C_{16}H_{18}O_4N_4$, which although closely similar are not identical. The non-identity of these 2 : 4-dinitrophenylhydrazones, which give no depression of the melting point on admixture, was confirmed by the fact that their *X*-ray powder photographs, kindly taken by Dr. T. Malkin, were slightly but definitely different. The intense colour of these compounds shows that they are derived from the αβ-unsaturated ketones (XI) and (XII). Should the olefinic bond in (X) be in the alternative position cyclisation might theoretically give rise to a *bicyclo*[5 : 2 : 1]decenone with an eight-membered ring, but this is considered improbable. The liquid ketone (XI) was first prepared by Hückel and Schnitzpahn by internal condensation of 1 : 6-diketo*cyclo*decane (*Annalen*, 1933, **505**, 274) and characterised by means of its crystalline oxime. We have been unable to obtain a solid oxime from either of our ketones, and it has thus been impossible to confirm the identity of their ketone previously described with either of ours.



(VIII.) (IX.) (X.) (XII.) (XI.)

During the course of this work we had occasion to make *trans-cyclo*pentane-1 : 2-dicarboxylic acid. This acid has previously been made from trimethylene dibromide *via* trimethylenebismalonic ester, cyclisation of the related disodio-derivative by treatment with bromine, and finally hydrolysis and decarboxylation (Perkin, *J.*, 1887, **51**, 240; 1894, **65**, 584; Uschakov, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 795; Kon and Nandi, *J.*, 1933, 1628; Guha and Seshriengar, *Ber.*, 1936, **69**, 1212). We find that the acid is more conveniently prepared from the readily available ethyl *cyclo*pent-1-enylcarboxylate (from *cyclo*pentanone cyanohydrin by dehydration and simultaneous hydrolysis and esterification; Cook and Linstead, *J.*, 1934, 959), by addition of the elements of hydrogen cyanide to the double bond, and hydrolysis of the cyano-ester. The *diamide* and *dinitrile* of *trans-cyclo*pentane-1 : 2-dicarboxylic acid are described.

EXPERIMENTAL.

Preparation of δ-Phenylvaleric Acid from 3-Phenylpropyl Bromide.—3-Phenylpropyl alcohol (136 g.) was refluxed for 4 hours with 48% hydrobromic acid (480 g.), the mixture cooled, diluted, and extracted with ether, and the extract washed with aqueous sodium carbonate, dried, and distilled, giving the bromide (170 g., 82%), b. p. 107—110°/8—9 mm. The procedure of Norris, Watt, and Thomas (*J. Amer. Chem. Soc.*, 1916, **38**, 1078) gives a 63% yield. Condensation of this bromide (80 g.) with ethyl malonate (von Braun and Kruber, *Ber.*, 1912, **45**, 386) gave ethyl 3-phenylpropylmalonate (70 g.; b. p. 180—195°/13 mm.), hydrolysis and decarboxylation of which gave finally δ-phenylvaleric acid, which after recrystallisation from light petroleum (b. p. 60—80°) had m. p. 57° (lit., 61°) (yield 30 g.).

Preparation of δ-Phenylvaleric Acid from Cinnamylidenemalonic Ester.—Cinnamaldehyde (82·5 g.), ethyl malonate (100 g.), benzene (200 c.c.), and piperidine (5 c.c.) were refluxed and slowly distilled till the calculated amount of water had collected (7½ hours). After cooling of the mixture, benzene (100 c.c.) was added and the solution washed successively with water, dilute hydrochloric acid, and sodium hydrogen carbonate solution, dried, and distilled, giving ethyl cinnamylidenemalonate, b. p. 188—190°/7 mm. (126 g.). Hydrolysis of this ester (172 g.) was effected by boiling aqueous sodium hydroxide (230 g. in 700 c.c.) (8—9 hours); water (500 c.c.) was then added, reduction carried out with Raney nickel alloy as described by Cook, Philip, and Somerville (*J.*, 1948, 164), and the resulting saturated acid decarboxylated, giving finally δ-phenylvaleric acid which, after purification as before, was obtained in colourless crystals, m. p. 60° (70 g.).

1 : *2-Benz*cyclo*hepten-3-one.*—The following method is based on that of Plattner (*Helv. Chim. Acta*, 1944, **27**, 804); it is carried out much more rapidly in almost twice the concentration but gives the same yield of benz*cyclo*heptenone. δ-Phenylvaleryl chloride (19·5 g.) in carbon disulphide (300 c.c.) was added (4 hours) to a stirred refluxing mixture of aluminium chloride (27·5 g.) and carbon disulphide (200 c.c.), and stirring was continued for 6 hours, after which the solvent was removed by distillation and the residue poured on ice (500 g.) and steam-distilled. The benz*cyclo*heptenone, isolated from the distillate by means of ether, was a liquid, b. p. 128—130°/6—7 mm. (14·0 g.).

*2′-Chloromethylbenz*cyclo*heptene* (II).—Benz*cyclo*heptene (56 g.), aqueous formaldehyde (35 c.c.; 40% solution), and concentrated hydrochloric acid (77 c.c.) were stirred vigorously at 60—70°, concentrated sulphuric acid (52 c.c.) was added dropwise during 7 hours, and stirring continued for a further 20 hours at the same temperature. The cooled mixture was then diluted with water and extracted with ether, and the extracts were washed with sodium hydrogen carbonate solution, dried, and distilled, giving two main fractions, (1) b. p. 60—120°/6 mm. (15 g.) consisting mainly of benz*cyclo*heptene, and (2) b. p. 120—133°/6 mm. (46 g.). Redistillation of fraction (2) gave *2′-chloromethylbenz*cyclo*heptene* (II) (40 g.), b. p. 138—141°/9 mm., n_D^{23} 1·5672 (Found: C, 73·8; H, 7·6; Cl, 18·7. $C_{12}H_{15}Cl$ requires C, 74·0; H, 7·7; Cl, 18·3%).

*2′-Cyanomethylbenz*cyclo*heptene.*—To (II) (35 g.) in ethanol (200 c.c.) was added a solution of potassium cyanide (23 g.) in water (50 c.c.), and the mixture refluxed for 5 hours. Dilution with water and extraction with ether yielded *2′-cyanomethylbenz*cyclo*heptene* (28 g.) as a colourless oil, b. p. 155—170°/10 mm., n_D^{16} 1·5518 (Found: C, 84·0; H, 8·1; N, 7·6. $C_{13}H_{15}N$ requires C, 84·3; H, 8·1; N, 7·6%).

*Benz*cyclo*heptene-2′-acetic Acid* (III).—2′-Cyanomethylbenz*cyclo*heptene (28 g.) was refluxed for 2 hours with water (25 c.c.), concentrated sulphuric acid (25 c.c.), and glacial acetic acid (25 c.c.). The mixture was diluted with water and extracted with ether, the extracts were shaken with dilute sodium hydroxide, the alkaline layer was acidified, and the precipitated *benz*cyclo*heptene-2′-acetic acid* (III) crystallised from aqueous acetic acid and then twice from light petroleum (b. p. 60—80°), giving fine needles (10·3 g.), m. p. 127° (Found: C, 76·6; H, 7·7. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). The *anilide* was prepared by heating the acid (1 g.) with thionyl chloride (1 c.c.) under reflux till reaction was complete, diluting the mixture with ether, and adding aniline (1 g.) slowly with cooling; the ethereal solution, after being washed with dilute hydrochloric acid, yielded a solid which when crystallised three times from benzene–light petroleum (b. p. 60—80°) gave fine, silky needles, m. p. 142—143° (Found: C, 81·3; H, 7·4; N, 5·4. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

*Ethyl Benz*cyclo*heptene-2′-acetate.*—(*a*) The preceding acid (10 g.) was refluxed with ethanol (100 c.c.) and concentrated sulphuric acid (3 c.c.) for 4 hours and the *ester* isolated in the usual way as a colourless oil (10·4 g.), b. p. 151—154°/4 mm., n_D^{17} 1·5282 (Found: C, 77·5; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%).

(*b*) 2′-Cyanomethylbenz*cyclo*heptene (28 g.) was refluxed for 18 hours with ethanol (105 c.c.) and concentrated sulphuric acid (10 c.c.), excess of ethanol removed under diminished pressure, water added, and the mixture extracted with ether. After being shaken with sodium hydrogen carbonate solution and drying, the ethereal layer yielded the ester (25 g.), b. p. 165—167°/9 mm.

Hydrolysis of the ester (25 g.) by boiling with potassium hydroxide (20 g.), water (20 c.c.), and ethanol (20 c.c.) for 4 hours yielded the free acid (III) which, after twice crystallising from dilute acetic acid and once from light petroleum (b. p. 60—80°), formed needles (13·2 g.), m. p. 127°.

Ethyl cyclo*Hexano*cyclo*heptane-2′-acetate.*—Ethyl benz*cyclo*heptene-2′-acetate (10·4 g.) in glacial acetic acid (100 c.c.) was shaken in hydrogen at atmospheric pressure in presence of Adams's platinum oxide catalyst (0·5 g.), rather more than the theoretical volume of hydrogen being absorbed in 72 hours.

After filtration the bulk of the solvent was removed under diminished pressure, the residue shaken with water and ether, and the ethereal layer shaken with sodium carbonate solution, dried, and distilled. *Ethyl* cyclo*hexano*cyclo*heptane-2′-acetate* was obtained as a colourless liquid (10·2 g.), b. p. 146—148°/4 mm., n_D^{15} 1·4826 (Found : C, 76·0; H, 10·8. $C_{15}H_{26}O_2$ requires C, 75·6; H, 10·9%).

(cis-?)cyclo*Hexano*cyclo*heptene-2′-acetic Acid* (IV).—The preceding ester (36 g.) was refluxed for 4 hours with potassium hydroxide (16 g.), water (40 c.c.), and ethanol (40 c.c.). After dilution, extraction with ether, and acidification, the semi-solid mass was collected and crystallised twice from light petroleum (b. p. 60—80°), giving cyclo*hexano*cyclo*heptane-2′-acetic acid* (IV) (11·5 g.) as small leaflets, m. p. 92—95° unaltered by further crystallisation (Found : C, 74·4; H, 10·6. $C_{13}H_{22}O_2$ requires C, 74·3; H, 10·5%). The light petroleum mother-liquors yielded a further quantity of the acid, b. p. 169—171°/0·5 mm. (9·5 g.), which crystallised on storage.

*2′-Aminomethyl*cyclo*hexano*cyclo*heptane* (V).—*cyclo*Hexano*cyclo*heptane-2′-acetic acid (9·5 g.), dissolved in concentrated sulphuric acid (18 c.c.), was covered with a layer of chloroform (90 c.c.) and vigorously stirred while sodium azide (3·6 g.) was slowly added. Stirring was then continued whilst the temperature was raised to 45°, and after evolution of gas was complete the mixture was poured on ice, made alkaline with sodium hydroxide, and extracted with ether. The extract yielded *2′-aminomethyl*cyclo*hexano*cyclo*heptane* (V) as an oil (7·1 g.), b. p. 108—110°/3 mm., n_D^{23} 1·5016 (Found : C, 79·7; H, 12·8; N, 7·6. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7; N, 7·7%). The *benzoyl* derivative, prepared by the Schotten–Baumann technique, was crystallised 3 times from aqueous ethanol and obtained as thin hexagonal plates, m. p. 129—131° (Found : C, 80·0; H, 9·7; N, 4·6. $C_{19}H_{27}ON$ requires C, 80·0; H, 9·5; N, 4·6%).

*Action of Nitrous Acid on 2′-Aminomethyl*cyclo*hexano*cyclo*heptane* (V). *Decahydroheptalene* (VI).—To the aminomethyl compound (V) (7·1 g.), dissolved in glacial acetic acid (3·5 c.c.) and water (70 c.c.), was added sodium nitrite (4·2 g.) in water (28 c.c.), and the mixture then heated on the water-bath until evolution of nitrogen had ceased. The oil which separated was extracted with ether, the extracts were washed with aqueous sodium hydroxide, dried, and distilled, giving two main fractions : (*a*) b. p. 53—93°/0·5 mm. (1·5 g.), and (*b*) b. p. 105—115°/1 mm., n_D^{19} 1·5022 (3·6 g.). Redistillation of fraction (*a*) over sodium gave *decahydroheptalene* (VI) as a colourless oil (1·0 g.), b. p. 58—62°/0·5 mm., n_D^{17} 1·5005, which became slightly brown when kept (Found : C, 87·2; H, 12·3. $C_{12}H_{20}$ requires C, 87·8; H, 12·1%). Fraction (*b*) probably consists mainly of 3-hydroxydodecahydroheptalene (VII) (Found : C, 77·8; H, 11·6. $C_{12}H_{22}O$ requires C, 79·1; H, 12·1%).

*Ethyl δ-(2-Keto-1-carbethoxy*cyclo*pentyl)valerate*.—Ethyl 2-keto*cyclo*pentane-1-carboxylate (24 g.) was added to powdered sodium (3·5 g.) and dry toluene (200 c.c.), and the mixture stirred till evolution of hydrogen had ceased (*ca.* 2 hours). Freshly distilled ethyl δ-iodovalerate (39 g.; Carter, *J. Amer. Chem. Soc.*, 1928, **50**, 1967) was then added, and the mixture stirred and refluxed for 16 hours. Water was added, and the toluene layer separated, washed with dilute sodium hydroxide solution, dried, and distilled, yielding *ethyl δ-(2-keto-1-carbethoxy*cyclo*pentyl)valerate* as a colourless oil (28 g.), b. p. 180—182°/4 mm. (Found : C, 63·6; H, 8·7. $C_{15}H_{24}O_5$ requires C, 63·4; H, 8·5%). This ester did not yield a crystalline 2 : 4-dinitrophenylhydrazone.

*Ethyl δ-2-Keto*cyclo*pentylvalerate* (VIII).—The preceding ester (25 g.) was refluxed for 8 hours with concentrated hydrochloric acid (50 c.c.), diluted, and extracted with ether. The extract (*A*) was shaken with excess of dilute aqueous sodium hydroxide. The alkaline layer yielded to ether crude δ-2-keto*cyclo*pentylvaleric acid (7·6 g.) as an oil which failed to crystallise, but which readily gave a 2 : 4-*dinitrophenylhydrazone* which was crystallised 5 times from benzene–light petroleum (b. p. 60—80°) and obtained as orange plates, m. p. 145—146° (Found : C, 53·4; H, 5·8; N, 15·6. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·5; N, 15·4%). The crude acid (7·4 g.) was refluxed for 4 hours with ethanol (100 c.c.) and concentrated sulphuric acid, and the ester isolated in the usual way, combined with that remaining in the ethereal extract (*A*), and distilled, yielding *ethyl δ-2-keto*cyclo*pentylvalerate* (VIII) (14·6 g.) as an oil, b. p. 124—125°/1·5 mm., $n_D^{17.5}$ 1·4567 (Found : C, 67·2; H, 9·9. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%). The 2 : 4-*dinitrophenylhydrazone* of this ester after crystallising twice from ethanol and once from methanol formed fine, orange-yellow plates, m. p. 78—79° (Found : C, 55·0; H, 6·1; N, 14·0. $C_{18}H_{24}O_6N_4$ requires C, 55·1; H, 6·1; N, 14·3%).

*Ethyl δ-2-Hydroxy*cyclo*pentylvalerate*.—To a solution of aluminium *iso*propoxide, made from aluminium foil (3·1 g.) and *iso*propyl alcohol (34 c.c.) by refluxing with a trace of mercuric chloride and carbon tetrachloride for 6 hours, was added ethyl δ-2-keto*cyclo*pentylvalerate (VIII) (8·1 g.) in *iso*propyl alcohol (50 c.c.). The mixture was refluxed and allowed to distil very slowly while *iso*propyl alcohol was added at the same rate; after 6 hours the distillate was free from acetone, and the solvents were then removed from the reaction mixture under diminished pressure. The product was then acidified with dilute hydrochloric acid and yielded to ether ethyl δ-2-hydroxy*cyclo*pentylvalerate as an oil (6·8 g.), b. p. 145—150°/4 mm. (Found : C, 69·1; H, 11·0. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%). This ester is not entirely homogeneous and probably contains some of the related unsaturated ester (below), and there is also the possibility of some ester exchange with the *iso*propyl alcohol.

*Ethyl δ-*cyclo*Pent-1-enylvalerate* (IX).—The preceding hydroxy-ester (6·5 g.) in anhydrous ether (60 c.c.) containing pyridine (4·9 g.) was slowly treated with thionyl chloride (3·7 g.) at 0°, and 4 hours later water was added, and the ethereal layer was washed with dilute hydrochloric acid and then with sodium carbonate solution, dried, and distilled. The *ester* (IX) was obtained as a yellow oil (5·0 g.), b. p. 150—160°/5—6 mm., n_D^{19} 1·4572 (Found: C, 73·8; H, 10·7. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%), which may contain some of the corresponding *iso*propyl ester. The free acid (X) obtained by hydrolysis with aqueous alcoholic potassium hydroxide was obtained as a pale yellow oil, b. p. 125—130°/1·6 mm.

*Cyclisation of δ-*cyclo*Pentylvaleric Acid* (X).—(*a*) (cf. Cook and Lawrence, *loc. cit.*). The crude acid (X) (1·5 g.) was converted into the chloride by the action of molecular quantities of thionyl chloride and pyridine in ether at 0°, filtration, and evaporation under diminished pressure. The chloride was treated in carbon disulphide solution with anhydrous stannic chloride in carbon disulphide at —10° and then allowed to reach room temperature overnight. After dilution the organic layer was washed with dilute sodium hydroxide solution and dried, the solvent removed under diminished pressure, and the residual oil heated with dimethylaniline for 3 hours at 180°. Addition of excess of dilute hydrochloric acid and extraction with ether yielded a brown oil (0·9 g.), which yielded a 2 : 4-*dinitrophenylhydrazone* which, after two crystallisations from ethyl acetate, formed fine, deep-red needles, m. p. 242—243° (Found : C, 58·9; H, 5·7; N, 16·7. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 17·0%). A crystalline oxime could not be obtained.

(*b*) (cf. Bachmann and Dreiding, *loc. cit.*). The crude acid (X) (2·9 g.) was dissolved in a solution of anhydrous zinc chloride (0·3 g.) in acetic acid (7 c.c.) and acetic anhydride (30 c.c.), and after 48 hours the mixture was heated to 70—80° for 1 hour and then well shaken with ether and dilute aqueous sodium hydroxide. The ethereal layer yielded a fraction (0·5 g.), b. p. 100—120°/2 mm., and a higher-boiling residue. The distillate gave a 2 : 4-dinitrophenylhydrazone which after 3 crystallisations from ethyl acetate formed fine, deep-red needles, m. p. 232° [the mixed m. p. with the 2 : 4-dinitrophenylhydrazone prepared by method (*a*) was 232°] (Found : C, 58·9; H, 5·6; N, 17·2%). Again, no crystalline oxime could be obtained.

trans-cyclo*Pentane*-1 : 2-*dicarboxylic Acid*.—Ethyl *cyclo*pent-1-ene-1-carboxylate (67 g.; Cook and Linstead, *loc. cit.*) in ethanol (250 c.c.) was refluxed for 4 hours with aqueous potassium cyanide (34 g. in 70 c.c.), after which aqueous potassium hydroxide (30 g. in 60 c.c.) was added and refluxing continued for a further 6 hours. Concentrated hydrochloric acid (100 c.c.) was then added and *cyclo*pent-1-ene-1-carboxylic acid removed in steam. When kept, the residual solution deposited *trans*-*cyclo*pentane-1 : 2-dicarboxylic acid which was crystallised from water giving the colourless acid (33 g.), m. p. 160°.

The acid (10 g.) was heated with thionyl chloride (20 c.c.) for 1 hour and then distilled and the di-acid chloride collected as an oil (10·5 g.), b. p. 98—100°/2 mm. This was added with shaking to aqueous ammonia (100 c.c.; *d* 0·88) at 0°. The *diamide* separated from water in highly refracting, rectangular prisms (6·6 g.), m. p. 303° (Found : C, 53·5; H, 7·6; N, 18·0. $C_7H_{12}O_2N_2$ requires C, 53·9; H, 7·7; N, 18·0%).

trans-1 : 2-*Dicyano*cyclo*pentane*.—The preceding diamide (6·6 g.) was refluxed for 2 hours with thionyl chloride (20 c.c.), excess of the reagent removed by distillation, and the residue dissolved in ether, shaken with aqueous sodium carbonate, dried, and distilled. The *dinitrile* (3·6 g.) was collected at 122°/6 mm. as an oil which set to a glassy mass on cooling (Found : C, 69·7; H, 6·9. $C_7H_8N_2$ requires C, 70·0; H, 6·7%).

The authors' thanks are offered to the Department of Scientific and Industrial Research for a maintenance allowance and to the directors of Monsanto Chemicals Ltd. for a Fellowship, which were held by one of us (G. O. A.), and also to Imperial Chemical Industries Ltd. for a grant which has met part of the costs incurred. The analyses are by Drs. Weiler and Strauss, Oxford.

THE UNIVERSITY, BRISTOL. [*Received, December 13th, 1949.*]

NOTES.

Preparation of N-*Bromosuccinimide by an Electrolytic Process.* By M. LAMCHEN.

FEW methods for the preparation of *N*-bromosuccinimide have been reported, viz., treatment of succinimide with *N*-bromoacetamide (Seliwanow, *Ber.*, 1893, **26**, 425), or with bromine and sodium hydroxide (Lengfeld and Stieglitz, *Amer. Chem. J.*, 1893, **15**, 215), or quickly brominating an ice-cold alkaline solution of succinimide (Ziegler *et al.*, *Annalen*, 1942, **551**, 80); 75—81% yields are reported in the latter process. *N*-Bromoacetamide used in the first method is obtained (Hofmann, *Ber.*, 1882, **15**, 408) by treating acetamide with bromine and ice-cold sodium hydroxide. All these methods thus employ bromine and sodium hydroxide, the function of which is to produce the hypobromite ion required for the reaction. Half of the bromine used is converted into bromide and is useless for the process; also, at least one equivalent of sodium hydroxide is consumed. In the process described below, hypobromite ions are produced without the use of bromine and with the use of only a small quantity of sodium hydroxide: an ice-cold solution of succinimide and sodium bromide is electrolysed between platinum electrodes with just sufficient sodium hydroxide to keep the solution colourless. Of every two bromide ions discharged at the anode, one again enters the solution as a bromide ion after reaction with hydroxyl ions. Thus, for every bromide ion discharged one molecule of *N*-bromosuccinimide is formed, one hydroxyl ion is produced, and one molecule of hydrogen is liberated. *N*-Bromosuccinimide alone has a low solubility in cold water and separates as a solid on the anode. Every bromide ion is effectively utilised, and the hydroxyl ions required are produced in the process.

The *N*-bromosuccinimide produced varies in colour from straw-yellow to white depending on the conditions used. The crude unwashed product melted at 163°, but by washing it once with a small quantity of ice-cold water the melting point is raised to 178·5°. Yields are 66% for the crude and 54% for the washed product.

The crude product could not be dissolved in benzene but after being washed with water it dissolved quite readily. The same phenomenon was observed with a sample of commercial material. The product is evidently covered with a layer of a benzene-insoluble, water-soluble substance. Ziegler also reported (*Annalen*, 1942, **551**, 80) that benzene was not satisfactory as a solvent for recrystallisation and used water. He considered the covering layer to be succinimide, but from the wash-liquor the present author could recover only *N*-bromosuccinimide. It is believed that the benzene-insoluble substance in this experiment may be sodium succinate because on evaporation of the filtrate at room temperature (or in a vacuum-desiccator) sodium succinate crystallises (its formation is to be expected).

Variation of the current density from 0·03 to 0·3 amp. per square inch made no difference to the reactions taking place in the process and the same products were obtained in all cases as long as it was low enough to avoid heating of the solution. At higher current densities the product was formed faster and was yellower, but yields were better. If the solution is allowed to become hot the yield drops very rapidly. The use of a rocking anode facilitated the peeling off of the product and gave a slightly better yield and a paler product.

Experimental.—Water was saturated with succinimide and an equimolecular amount of sodium bromide was then dissolved in the solution. This solution was electrolysed between platinum electrodes, at a current density of 0·3 amp. per sq. in., in an ice-bath, and 10% sodium hydroxide solution was added drop by drop till the solution no longer became brown. The anode, if stationary, was shaken at intervals to allow the *N*-bromosuccinimide to drop off; a rocking anode was generally used. When 10 g. of succinimide were used with electrodes 1½ in. square, 3—4 hours sufficed for completion of the reaction. The bulk of the yield was formed during the first hour. 10 G. of crude product, m. p. 163°, were obtained. After filtration, 10 g. of succinimide and 10·3 g. of sodium bromide were dissolved in the filtrate, and the solution was again electrolysed, giving a further yield of 11·85 g. (66%) (m. p. 163°).—University of Cape Town, South Africa. [*Received, August 15th,* 1949.]

Preparation of N-*Acetyl*-N-*methylurea by an Electrolytic Process.* By M. Lamchen.

The electrolytic method for the preparation of *N*-bromosuccinimide described by the author (preceding note) indicated that imido-hydrogen atoms could be substituted by bromine atoms during electrolysis of an aqueous solution of an imide, sodium bromide, and a small quantity of sodium hydroxide. When the electrolysis is carried out in an ice-cold solution the reaction proceeds only as far as the *N*-bromo-imide which, if fairly insoluble in water, is precipitated. This was the case with *N*-bromosuccinimide; when, however, a saturated ice cold solution of acetamide, containing sodium bromide and sufficient sodium hydroxide to keep it colourless, was electrolysed for 10 hours, *N*-bromoacetamide, being soluble, did not crystallise from the solution.

An *N*-bromo-amide would lose hydrogen bromide in warm sodium hydroxide solution, to form the *iso*cyanate (cf. the Hofmann degradation of amides), which would react with suitable compounds. If thus the electrolysed solution of acetamide, sodium bromide, and sodium hydroxide is allowed to become hot, or if the electrolysis is carried out without cooling, the *N*-bromoacetamide, if formed, should lose hydrogen bromide to give methyl *iso*cyanate. In practice white crystals soon appeared and more separated after cooling. These were identified (mixed m. p.) as *N*-acetyl-*N*-methylurea, formed by reaction of the methyl *iso*cyanate with unchanged acetamide.

From a fresh solution 67% yields, calculated on the acetamide, were obtained, but if the filtrate of a previous experiment was used 70—80% yields were obtained. The product is almost pure and is quite white.

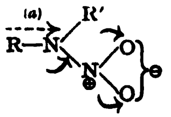
Previous methods are those of Young and Clark (*J.*, 1898, **73**, 364; methylamine is treated with acetylurethane) and of Odendal (*Annalen*, 1918, **416**, 228; acetamide is heated with bromine and sodium hydroxide until the solution becomes acid and yellow). Odendal records yields of up to 75%, but the pH is critical and if the solution is slightly too alkaline the yield drops to zero and the process proceeds in a different way. For every molecule of acetamide he used one molecule of sodium hydroxide and more than one molecule of bromine. The electrolytic process described above eliminates the use of bromine and requires only small quantities of sodium hydroxide as the bulk of the required hydroxyl ions are obtained from the electrolysis of the solution; also all the bromide ions should be available for the process and the subsequent splitting off of hydrogen bromide should again regenerate the bromide ions.

Variations of current densities between 0·03 and 0·3 amp. per sq. in. made no difference to the product except that it was formed much faster and yields were better at the higher current densities.

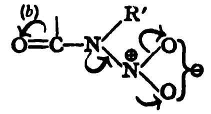
Experimental.—A saturated solution containing acetamide (30 g.) and sodium bromide (15 g.) is electrolysed between platinum electrodes at 0·3 amp. per sq. in. with just sufficient sodium hydroxide (10%) added to prevent the solution becoming brown. Further small quantities of sodium hydroxide may be needed later. Crystals form in the solution after ¼—1 hour, depending on the current density. After about 10 hours the solution was cooled and filtered, and the product (20·2 g.) was washed with ice-cold water. After recrystallisation from benzene it had m. p. 180—181° (Found: C, 41·6; H, 6·8. Calc. for $C_4H_8O_2N_2$: C, 41·4; H, 6·9%).—University of Cape Town, S. Africa. [*Received, August 15th,* 1949.]

The Hydrolysis of NN′-*Dinitro-oxamide*-NN′-*bis*-(2-*ethyl Nitrate*). By J. Vaughan.

The preparation and properties of this dinitrate (III) have been investigated by Wright *et al.* (*e.g.*, Stuart and Wright, *Canadian J. Res.*, 1948, **26**, *B*, 401). The hydrolysis of this compound is of interest because on theoretical grounds it appears that aqueous hydrolysis should proceed quite readily. When the group $-NR'\cdot NO_2$ is linked to an alkyl group R, as in (I), the new R–N linkage should be relatively stable because the electrophilic tendency of the amino-nitrogen atom can be partly met by the electron-donating effect (*a*) of the alkyl group. When the group $-NR'\cdot NO_2$ is linked to a carbonyl group, as in (II), the electrophilic tendency of the amino-nitrogen atom and the electromeric effect (*b*), caused by the



(I.)



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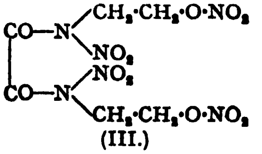
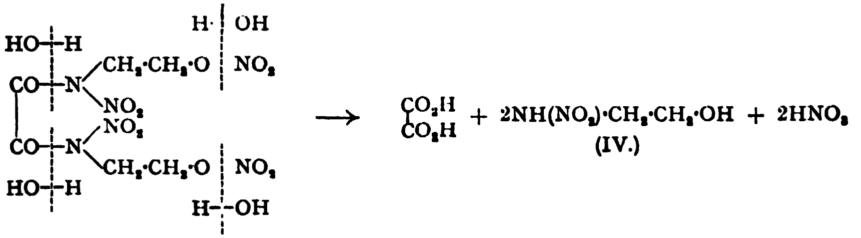


(III.)

strong displacement towards the carbonyl oxygen, combine to make the carbonyl carbon susceptible to nucleophilic attack. The carbonyl–N linkage in (II) should thus be relatively unstable to hydrolysis. This argument is supported by the fact that ethylenedinitroamine, a compound of type (I), is very much more stable to hydrolysis than nitrourea, a compound of type (II). Ethylenedinitroamine may be prepared by the action of boiling water on dinitroethyleneurea (Franchimont and Klobbie, *Rec. Trav. chim.*, 1888, **7**, 17), but nitrourea is readily decomposed by hot water and the decomposition is accelerated by the presence of bases (Sidgwick's "Organic Chemistry of Nitrogen," 1937, p. 280). Compound (III), like nitrourea, should be fairly readily attacked by warm water, but the possibility of the alkyl nitrate groupings also undergoing hydrolysis is to be borne in mind.

Preliminary experiments on the hydrolysis of (III), which is insoluble in water, have been carried out at 49° with a stationary amide–water interface. The results can be summarised as follows: (i) the acidity developed is, approximately, accounted for by the oxalic and nitric acids formed; (ii) within the limits of experimental error the *molar* ratio of nitric to oxalic acid formed is 2 : 1.

On the basis of these preliminary results, therefore, the hydrolysis of the substituted oxamide can be represented thus



$$\xrightarrow{} \begin{matrix}CO_2H\\CO_2H\end{matrix} + 2NH(NO_2)\cdot CH_2\cdot CH_2\cdot OH + 2HNO_3$$

(IV.)

Monoethanolnitroamine (nitro-2-hydroxyethylamine) (IV) contains an acidic hydrogen atom; it might be expected, therefore, that this would be estimated in the total acidity. However, in the presence of acids, this compound is readily decomposed into ethylene glycol and nitrous oxide (Franchimont, *Rec. Trav. chim.*, 1902, **21**, 50). It was established during the present work that nitrous oxide was formed during the hydrolysis in amount corresponding to at least two-thirds of the theoretical.

Experimental.—Hydrolysis was followed by determination of the loss in weight of the amide and estimation of hydrolysis products. The substituted oxamide was recrystallised from acetone, dried *in vacuo* over phosphoric oxide, and passed through a 100-mesh B.S. sieve. Portions (0·5 g.) were each placed in contact with distilled water (40 ml.) in 100-ml. conical Pyrex flasks fitted with standard ground-glass stoppers. 0·01 G. of lauryl alcohol was also added in each case in order to get thorough wetting of the crystals, and the flasks were then placed in a thermostat at 49°. Although the lauryl alcohol would probably increase the rate of hydrolysis, it was considered unlikely that the course of hydrolysis would be affected. In this way an approximately constant initial area of interface between amide and water could be assumed.

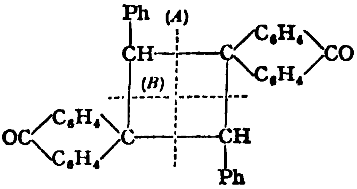
Flasks were removed at intervals, and the solid residue filtered off. This was dried and weighed, and the m. p. of each precipitate indicated that pure (III) had been recovered. The filtrates in each case gave positive tests for the presence of oxalic and nitric acids. The complete filtrate then underwent the following sequence of determinations: (i) of total acidity by titration, (ii) of oxalic acid as calcium oxalate by permanganate, (iii) of nitric acid by "nitron." In no case could more than a trace of nitrous acid be detected in the filtrate, using the Griess–Ilosvay reagent. The results are summarised in the table.

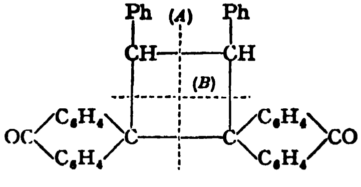
Time (days) at 49°.	Wt. of compound taken (g.).	% not hydrolysed.	Total acidity (ml., N/10).	Nitric acid (ml., N/10).	Oxalic acid (ml., N/10).
4	0·4995	not determined	17·4	9·1	9·4
8	0·5002	51·9	29·3	16·8	15·1
12	0·5000	26·9	40·7	19·6	19·5
17	0·5087	20·4	46·8	22·6	24·9
25	0·5021	14·3	48·6	24·4	25·1

The author thanks the Chief Scientist of the Ministry of Supply for permission to publish this work, which was carried out in the Armament Research Department of the Ministry in 1945.—CANTERBURY UNIVERSITY COLLEGE, CHRISTCHURCH, NEW ZEALAND. [*Received, September 29th,* 1949.]

Reactions in Sunlight. By FAWZY GHALI BADDAR.

MUSTAFA and ISLAM (*J.*, 1949, S 81) claimed that the dimer obtained by exposing 9-benzylideneanthrone in benzene solution to sunlight has the structure (II) because (i) it lacks colour, (ii) on being heated at 270° it regenerates the monomer, and (iii) it has the correct molecular weight. The product may equally, however, have the isomeric structure (I), which would give only 9-benzylideneanthrone on thermal decomposition, whether cleavage of the bonds occurs along (*A*) or along (*B*); if it has the isomeric structure (II), thermal decomposition would give rise to a mixture of the monomer, stilbene, and dianthraquinonyl. Stobbe and Bremer (*J. pr. Chem.*, 1929, **123**, 1) isolated two dimers of benzylideneacetophenone; that which gave stilbene on thermal decomposition was given a structure analogous to (II), whereas that which gave mainly the monomer was assigned a structure analogous to (I). The fact that the above authors failed to isolate any stilbene among the decomposition products supports structure (I) rather than (II).


(I.)


(II.)

Similarly, in the photo-reactions between retenequinone and 9-benzylidenexanthen or methyleneanthrone and between chrysenequinone and triphenylethylene (Mustafa, *J.*, 1949, S 83), the constituent molecules can theoretically unite in two ways to give two isomerides, which would give identical products on thermal decomposition.—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, ABBASSIA, CAIRO, EGYPT. [*Received, October 5th,* 1949.]

3-*Hydroxy*-4 : 5-*dimethoxybenzoic Acid Derivatives.* By J. R. ANSTEE and D. E. WHITE.

3-HYDROXY-4 : 5-DIMETHOXYBENZOIC ACID has been synthesised from gallic, 5-nitroveratric, and 5-bromoveratric acid. Späth and Röder's method starting from gallic acid (*Monatsh.*, 1922, **43**, 93) is most convenient for the preparation of the acid in quantity; the acid has been characterised by the acetyl derivative, which melts 10° higher than that prepared by Shriner and McCutchan (*J. Amer. Chem. Soc.*, 1929, **51**, 2193) from a low-melting sample of 3-hydroxy-4 : 5-dimethoxybenzoic acid.

Ethylation with ethyl sulphate and alkali gave 3 : 4-dimethoxy-5-ethoxybenzoic acid, m. p. 117—118°. Seshadri and Venkateswarlu (*Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 296) describe this acid as melting as 164°, only 3° lower than their sample of trimethylgallic acid. This m. p. appears to be in error as the isomeric 3 : 5-dimethoxy-4-ethoxybenzoic acid (Bogert and Ehrlich, *J. Amer. Chem. Soc.*, 1919, **41**, 801) melts more than 40° lower than trimethylgallic acid.

Methyl and *ethyl* 3 : *4-dimethoxy-5-ethoxybenzoate* were prepared with the appropriate alcohol and sulphuric acid.

Experimental (M. p.s are corr.).—*3-Hydroxy-*4 : *5-dimethoxybenzoic acid.* Prepared by the method of Späth and Röder (*loc. cit.*), this acid formed colourless needles (from water), m. p. 195—196°, considerably depressed by admixture of syringic acid (m. p. 207°). When refluxed (1 g.) with acetic anhydride (5 ml.) and pyridine (1 drop) for 30 minutes, it gave an acetyl derivative (1 g.), isolated by pouring the mixture into water and forming long colourless prisms (from aqueous methyl alcohol), m. p. 148° (Found : C, 55·05, H, 5·2. Calc. for $C_{11}H_{12}O_6$: C, 55·0; H, 5·0%), considerably depressed by admixture with acetylsyringic acid (m. p. 184—186°).

3 : *4-Dimethoxy-5-ethoxybenzoic acid.* The above acid (18 g.) in 10% sodium hydroxide solution (80 ml.) was boiled under reflux during the addition, during 30 minutes, of ethyl sulphate (40 ml.) and 10% sodium hydroxide solution (132 ml.). Refluxing was continued for 1 hour, and ethyl sulphate (26 ml.) and 20% sodium hydroxide solution (40 ml.) added during the next 15 minutes. After refluxing for a further 30 minutes, ethanol (17 ml.) was removed by distillation, and the solution treated with charcoal, cooled, and acidified with hydrochloric acid. The acid (20 g.) formed colourless needles and plates from 10% alcohol (800 ml.) and after two crystallisations melted constantly at 117—118° (15 g.) (Found : C, 58·5; H, 6·35. Calc. for $C_{11}H_{14}O_5$: C, 58·4; H, 6·2%).

Methyl and ethyl esters. A solution of 3 : 4-dimethoxy-5-ethoxybenzoic acid (5 g.) in the appropriate alcohol (50 ml.) was refluxed with sulphuric acid (0·2 ml.) for 8 hours and the ester isolated by distillation of the alcohol, dissolution of the residue in ether, and washing of the extract to remove acids. After drying (Na_2SO_4) and distillation of the ether the ester remained. The *methyl* ester crystallised as colourless needles, m. p. 51·5° (2·5 g.) (Found : C, 60·09; H, 6·76. $C_{12}H_{16}O_5$ requires C, 59·98; H, 6·71%), from 40% methyl alcohol. The *ethyl* ester was a colourless oil, b. p. 139—140°/3 mm., 105—106°/0·1 mm., n_D^{16} 1·5268, n_D^{23} 1·5160 (2·2 g.) (Found : C, 61·5; H, 7·4. $C_{13}H_{18}O_5$ requires C, 61·3; H, 7·1%).

The authors acknowledge financial support from the Commonwealth Research Grant to Australian Universities and microanalyses by Drs. Weiler and Strauss.—UNIVERSITY OF WESTERN AUSTRALIA. [*Received, October 24th,* 1949.]

Certain Substituted Benzaldehydes and Substituted Benzaldehyde Dinitrophenylhydrazones.

By J. B. BOWEN and E. M. WILKINSON.

DURING investigations on the adsorption of 2 : 4-dinitrophenylhydrazones on activated alumina, a series of substituted benzaldehyde 2 : 4-dinitrophenylhydrazones was prepared. Nine of these derivatives are new and it therefore seemed desirable to record the new data. The Stephen reduction of nitriles (*J.*, 1925, **127**, 1874) has been applied for the first time to the synthesis of four of the aldehydes used. These preparations are briefly recorded.

m-*Tolualdehyde.*—*m*-Tolunitrile (8·7 g.) was added to anhydrous stannous chloride (25 g.) dissolved in dry ether (50 c.c.) saturated with dry hydrogen chloride. After 2 days the crystals which had deposited were filtered off and steam-distilled. The aldehyde was ether-extracted from the distillate, dried, and distilled in an atmosphere of carbon dioxide. B. p. 198°/756 mm. Yield, 50%. Von Auwers (*Annalen*, 1915, **408**, 237) gives b. p. 195°/745 mm.

m-*Chlorobenzaldehyde.*—*m*-Chlorobenzonitrile (2·9 g.) and stannous chloride (10 g.) in dry ethereal hydrogen chloride (30 c.c.) gave similarly, after 24 hours, the aldehyde of b. p. 213—214° (53%). Erdmann and Schwechten (*ibid.*, 1890, **260**, 59) give b. p. 213—214°.

p-*Bromobenzaldehyde.*—*p*-Bromobenzonitrile (10 g.) and stannous chloride (21 g.) in dry ethereal hydrogen chloride (200 c.c.), when kept overnight, gave an aldehyde which, when similarly isolated and then recrystallised from dilute methanol, had m. p. 57° (62%). Adams and Vollweiler (*J. Amer. Chem. Soc.*, 1918, **40**, 1738) give m. p. 56—57°.

p-*Iodobenzaldehyde.*—*p*-Iodobenzonitrile (10 g.) in dry ether (50 c.c.) with saturated, dry, ethereal hydrogen chloride solution (150 c.c.) containing anhydrous stannous chloride (40 g.) gave similarly, after 24 hours, the aldehyde (56%), m. p. 77° (from aqueous ethanol). Willgerodt and Bogel (*Ber.*, 1905, **38**, 3451) give m. p. 78°.

In some cases more crystals of the aldimine stannichloride were deposited in the reaction flask on further storage, so that the yields could be improved a little if necessary.

The Sandmeyer procedure described by Clark and Read (*Org. Synth.*, Coll. Vol. I, p. 514) for the preparation of *o*- and *p*-tolunitrile was applied to obtain the necessary *m*-tolunitrile, *m*-chloro-, *p*-bromo-, and *p*-iodo-benzonitrile in 53, 59, 67, and 68% yield, respectively, from the appropriate amines.

Preparation of the Dinitrophenylhydrazones.—Except where otherwise stated, the general procedure for the preparation of these derivatives was to add a solution of the aldehyde in methanol to a slight excess of the reagent dissolved in sulphuric acid–methanol (1 : 10) or dilute hydrochloric acid. The derivatives so obtained were repeatedly recrystallised to constant m. p. using, in most cases, two different solvents in succession, and dried *in vacuo* at 100° for analysis. The *m*-amino-compound is an exception in this respect, in that we failed to recrystallise it in a satisfactory manner without decomposition. The solubilities in benzene at room temperature were determined by using a Spekker photoelectric absorptiometer to measure concentrations. The tungsten lamp in conjunction with the usual heat filters and "Ilford 601" violet filters were suitable for all the solutions examined.

M. p.s were determined by using short-range Anschütz-type thermometers and are corrected except where otherwise specified.

m-*Aminobenzaldehyde* 2 : 4-*dinitrophenylhydrazone.* *m*-Aminobenzaldehyde was prepared *in situ* by Buck and Ide's method (*Org. Synth.*, Coll. Vol. II, p. 130), and its solution in aqueous hydrochloric acid added directly to a saturated solution of the reagent in the same medium. The brownish-red precipitate of the *dinitrophenylhydrazone* was washed with distilled water until free from chloride ions and dried in a vacuum desiccator. Solubility in benzene, 13 mg./100 ml. It decomposes from about 230° (Found : N, 23·0. $C_{13}H_{11}O_4N_5$ requires N, 23·3%).

p-*Aminobenzaldehyde* 2 : 4-*dinitrophenylhydrazone.* *p*-Aminobenzaldehyde, prepared *in situ* from *p*-nitrotoluene by Beard and Hodgson's method (*J.*, 1944, 4), was used immediately in dilute acid solution as described for *m*-aminobenzaldehyde. The precipitated *dinitrophenylhydrazone* was thoroughly washed until free from mineral acid and was obtained as a light-brown powder, m. p. 192·5—194·5° (slight decomp.), after recrystallisation from methanol (Found : N, 23·4. $C_{13}H_{11}O_4N_5$ requires N, 23·3%).

m-, bright yellowish-orange crystals (from aqueous pyridine and then from xylene) (solubility in benzene, 34 mg./100 ml.), m. p. 256—257° (Found : N, 15·2. $C_{13}H_9O_4N_4Br$ requires N, 15·3%), and p-*bromobenzaldehyde* 2 : 4-*dinitrophenylhydrazone,* bright orange crystals (from aqueous pyridine and then from xylene) (solubility in benzene, 25 mg./100 ml.), m. p. 256—257·5° (Found : N, 15·5%), were obtained by the general method.

p-*Carboxybenzaldehyde* 2 : 4-*dinitrophenylhydrazone* was prepared by adding the reagent in hot dilute hydrochloric acid to the aldehyde in the same solvent. The precipitated derivative was filtered hot and obtained as bright light-orange crystals from aqueous pyridine. It was further recrystallised from nitrobenzene. It was practically insoluble in benzene. M. p. 319·5—320·5° (uncorr.) (Found : N, 17·1. $C_{14}H_{10}O_6N_4$ requires N, 17·0%).

p-*Iodobenzaldehyde* 2 : 4-*dinitrophenylhydrazone* was obtained by the general method. The precipitated derivative was washed with boiling dilute hydrochloric acid and then with water. After recrystallisation from an aqueous pyridine–methanol and finally from xylene it yielded pale orange-brown crystals (solubility in benzene, 38 mg./100 ml.), m. p. 256·5—257·5° (Found : N, 13·7. $C_{13}H_9O_4N_4I$ requires N, 13·6%).

The standard method yielded 2 : 4-*dinitrophenylhydrazones* from *p*-carbomethoxybenzaldehyde, pale-orange, m. p. 263·5—265° (from aqueous pyridine) (Found : N, 16·4. $C_{15}H_{12}O_6N_4$ requires N, 16·2%) (solubility in benzene, 14 mg./100 ml.), *m*-methoxybenzaldehyde, brilliant red crystals (from pyridine and then from xylene) (solubility in benzene, 32·5 mg./100 ml.), m. p. 218·5—219·5° (Found : N, 17·7. $C_{14}H_{12}O_5N_4$ requires N, 17·7%), and *m*-tolualdehyde, bright orange-red crystals (from aqueous pyridine and then from xylene) (solubility in benzene, 152 mg./100 ml.), m. p. 211·5—212·5° (Found : N, 18·8. $C_{14}H_{12}O_4N_4$ requires N, 18·7%).

One of us (J. B. B.) gratefully acknowledges his indebtedness to the Chemical Society for a research grant and the other (E. M. W.) to the Department of Scientific and Industrial Research for a maintenance grant.—The Edward Davies Chemical Laboratories, University College of Wales, Aberystwyth. [*Received, October 31st, 1949.*]

The Resolution of p-*Chlorobenzhydrol.*

By G. H. Green and J. Kenyon.

The main object in resolving *p*-chlorobenzhydrol into its optical isomerides was to compare the readiness with which alkyl–oxygen fission occurred during reactions of this compound and its derivatives with that of *o*-chlorobenzhydrol and its corresponding derivatives. The latter compounds were shown (Balfe *et al.*, *J.*, 1946, 797) to exhibit only negligible alkyl–oxygen fission due, doubtless, to the deactivating influence of the chlorine substituent. For this reason and also because it was found that *p*-chlorobenz-

hydryl hydrogen phthalate undergoes hydrolysis to the carbinol with extreme readiness further investigation of the reactions of *p*-chlorobenzhydrol and its derivatives was not proceeded with.

***Experimental.*—*p*-Chlorobenzhydrol was readily obtained in good yield by the reduction of *p*-chlorobenzophenone with either aluminium *iso*propoxide or, very conveniently, with zinc dust (an equal weight) and alcoholic sodium hydroxide (10 vols.; 10%). It separated from light petroleum in needles, m. p. 58·5—59·5°.**

(±)-p-***Chlorobenzhydryl hydrogen phthalate.*** A solution of phthalic anhydride (15 g.) in boiling anhydrous pyridine (10 g.) was rapidly cooled to about 50° and mixed with *p*-chlorobenzhydrol (20 g.), and the whole mass thoroughly stirred; it gradually stiffened and set solid within a few hours. It was then heated at 60° for 2 hours, cooled, and dissolved in acetone and the solution poured, with stirring, into water containing a slight excess of hydrochloric acid. The resulting solid was dissolved in ether, extracted therefrom with sodium carbonate (5%), and finally precipitated with cold dilute hydrochloric acid. (±)-p-***Chlorobenzhydryl hydrogen phthalate*** separated from benzene in needles, m. p. 152° [Found (by titration in acetone–ethanolic solution with N/10-NaOH): *M*, 366·8. $C_{21}H_{15}O_4Cl$ requires *M*, 366·8].

(−)-p-***Chlorobenzhydryl hydrogen phthalate.*** The only reasonably successful procedure for obtaining this compound appears to be to leave a solution of the brucine salt of the (±)-ester in ethyl acetate to evaporate at room temperature until a suitable amount of crystallisation has occurred.

A solution of the (±)-hydrogen phthalate (55 g.) and brucine (59·4 g.) in dry ethyl acetate (275 c.c.) was divided between eleven conical flasks (100 c.c.), each containing a " seed " of brucine salt, and left uncovered during 4 days. The various crystalline crops, m. p. 113° (decomp.), were separated by decantation of the mother liquors and each recrystallised twice more by the same procedure. Further recrystallisation was precluded owing to progressive decomposition of the salt, presumably by hydrolysis, into *p*-chlorobenzhydrol and brucine hydrogen phthalate. The recrystallised brucine salt was dissolved in acetone and decomposed with cold dilute hydrochloric acid, and the liberated acid ester purified by solution in sodium carbonate as described above (yield, 9 g.; m. p. 135°). It suffered no change either in m. p. or rotatory power by crystallisation from benzene.

(+)-p-***Chlorobenzhydryl hydrogen phthalate.*** The combined mother liquors from the first crystallisation of the brucine salt on storage deposited two further small crops of salt which were removed by filtration. This final filtrate on decomposition yielded the (+)-acid ester (15 g.), m. p. 146°, $[\alpha]_{5461}$ +1·1° (*l*, 1·0; *c*, 26·7 in acetone solution).

(−)-p-***Chlorobenzhydrol.*** The (−)-acid phthalic ester (5 g.) in hot methanol (50 c.c.) was mixed with sodium hydroxide solution (5 c.c.; 40%) and the whole heated on the steam-bath for 10 minutes. Water (200 c.c.) was added to the cooled solution to dissolve the precipitated sodium hydrogen phthalate, and the liberated carbinol was extracted with ether. It (3 g.) had m. p. 54—56°, unchanged by crystallisation from light petroleum.

(+)-p-***Chlorobenzhydrol.*** The (+)-acid ester (7 g.) by similar treatment yielded (+)-*p*-chlorobenzhydrol (4 g.), m. p. 50—54°.

Specific rotatory powers (*l*, 1·0; temp. 20°).

Solvent.	*c*, g./100 c.c. of solution.	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.	Solvent.	*c*, g./100 c.c. of solution.	$[\alpha]_{5893}$.	$[\alpha]_{5780}$.	$[\alpha]_{5461}$.
(−)-*p*-Chlorobenzhydryl hydrogen phthalate.					(+)-*p*-Chlorobenzhydrol.				
Chloroform ...	13·3	−3·5°	−3·7°	−4·9°	Chloroform	20·0	+13·7	+14·1	+15·5
Acetone	13·3	3·8	4·2	4·2					
(−)-*p*-Chlorobenzhydrol.									
Acetone	13·3	18·7	20·4	21·7	Chloroform	6·7	32·1	34·1	38·0
Ethanol (99%)	6·7	18·9	20·3	22·2	Benzene ...	6·7	29·9	31·5	34·8
Ethyl acetate	6·7	23·4	24·3	27·6					

We have pleasure in expressing our thanks to Imperial Chemical Industries Ltd. for a grant.—
BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, November* 4th, 1949.]

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p-*Bishalogenoacetylbenzenes.* By W. C. J. Ross.

DURING the examination of possible cytotoxic substances containing two or more groupings capable of reacting with functional centres in biological systems (Everett and Ross, *J.*, 1949, 1972; Goldacre, Loveless, and Ross, *Nature*, 1949, **163**, 667) the preparation of *p*-bishalogenoacetylbenzenes was undertaken. These compounds had previously been prepared by Ruggli and Gassenmeier (*Helv. Chim. Acta*, 1939, **22**, 496) by direct halogenation of *p*-diacetylbenzene which was obtained by the sequence of reactions: *p*-xylene ⟶ terephthalic acid ⟶ terephthaloyl chloride ⟶ terephthalyldiacetoacetic ester ⟶ diacetylbenzene. The required compounds can be prepared more directly by the following route: terephthaloyl chloride ⟶ *p*-bisdiazoacetylbenzene ⟶ bishalogenoacetylbenzene.

p-*Bisdiazoacetylbenzene.* Terephthalic acid (3 g.), thionyl chloride (10 ml.), and pyridine (1 drop) were heated on a steam-bath for 3 hours. Dry benzene (30 ml.) was added, and the mixture was evaporated under reduced pressure. The chloride (2 g.), m. p. 82—84°, crystallised from light petroleum (b. p. 60—80°). Terephthaloyl chloride (1·5 g.) dissolved in dry ether (50 ml.) was gradually added to an ice-cooled ethereal (200 ml.) solution of diazomethane [from nitrosomethylurea (5 g.)]. Next day, the dense yellow precipitate (2 g.) was collected and recrystallised from benzene. It formed short needles, decomp. >370° when slowly heated but melting with decomp. when placed in a bath at 200°

(Found: C, 56·4; H, 3·2. $C_{10}H_6O_2N_4$ requires C, 56·1; H, 2·8%. The *diazo*-compound is difficult to analyse since it explodes on heating).

p-*Bishalogenoacetylbenzenes.* (*a*) The diazo-ketone (1 g.) was suspended in ether (50 ml.) and treated with concentrated hydrochloric acid (0·5 ml.). After the evolution of nitrogen had subsided the chloroacetyl compound separated. It formed needles, m. p. 186°, from methanol (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 153°) (Found: C, 52·0; H, 3·6. Calc. for $C_{10}H_8O_2Cl_2$: C, 52·0; H, 3·5%). (*b*) *p*-Bisbromoacetylbenzene, prepared similarly, formed prismatic needles, m. p. 176—177°, from methanol (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 173°). (*c*) The bromo-ketone (500 mg.) and sodium iodide (500 mg.) in acetone (10 ml.) were warmed on a steam-bath for 10 minutes. The iodo-compound which separated on adding water gave needles, m. p. 135°, from aqueous methanol (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 135°).

This investigation was carried out during the tenure of a Sir Halley Stewart Fellowship.—THE CHESTER BEATTY RESEARCH INSTITUTE, FULHAM ROAD, LONDON, S.W.3. [*Received, December 1st,* 1949.]

Acetylene and Acetylenic Compounds in Organic Synthesis.

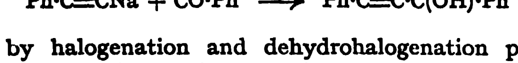
THE TILDEN LECTURE, DELIVERED BEFORE THE SOCIETY AT THE IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, ON OCTOBER 20TH, 1949.

By E. R. H. JONES, D.Sc., F.R.I.C.

RECENT developments in acetylene chemistry have been many and varied and, as a result, the opportunities for the use of acetylene and acetylenic compounds in synthetic work have been greatly extended. The advantages to be gained by employing these versatile and reactive compounds are not too widely appreciated and consequently when this lecture was first planned, more than two years ago, it had been intended to attempt a broad review of the whole field. In the meantime, however, several aspects of the subject have been admirably dealt with (Johnson, "Some Applications of Acetylenic Compounds in Organic Synthesis," R.I.C., 1948; Bergmann, "Acetylene Chemistry," 1948; Sir Ian Heilbron, Pedler Lecture, *J.*, 1948, 386; Reppe, *Experientia*, 1949, **5**, 93), and this lecture is therefore somewhat more restricted in its scope than would otherwise have been the case. Even with this almost welcome limitation the selection of topics has been by no means easy and to a large extent the examples chosen to illustrate the general theme have been taken from recent work in the laboratories at Imperial College, London, and at Manchester University.

Although the original discovery of acetylene was made by Davy more than a hundred years ago, and many of its reactions and those of simple acetylenic compounds were investigated from 1860 onwards, especially by Berthelot and his school, it was not until the turn of the century that acetylene became readily available with the introduction of a method for the manufacture of calcium carbide. In the first instance, this availability of carbide led to the widespread use of acetylene as an illuminant (1894), to the utilisation of the cyanamide process for nitrogen fixation (1904), and to the employment of the oxy-acetylene flame (1906). The potentialities for organic syntheses, realised by Berthelot as early as 1872, were to remain largely unexploited for many years. It was not until World War I that the conversion of acetylene into acetaldehyde, long studied in the laboratory, was realised commercially, and during World War II many processes based on acetylene, but not competitive under normal conditions, were operated on a large scale in Germany. The remarkable work of Reppe and his collaborators, revealing so many novel and fascinating reactions in the field of acetylene chemistry emanated largely from the need for the utilisation of acetylene as a major starting material for the German organic chemical industry.

At just about the time when carbide became readily available, Nef (*Annalen*, 1899, **308**, 264) discovered a reaction which, probably more than any other, has fostered the employment of acetylenic compounds in synthetic work. Reasoning from analogy with the zinc alkyls he demonstrated that the sodium derivative of phenylacetylene could be condensed with carbonyl compounds to give acetylenic carbinols (*e.g.*, I), previously available only from the corresponding



$$\mathrm{Ph{\cdot}C{\equiv}CNa} + \overset{\mathrm{CH_3}}{\mathrm{CO{\cdot}Ph}} \longrightarrow \mathrm{Ph{\cdot}C{\equiv}C{\cdot}}\overset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{(OH){\cdot}Ph}$$

(I.)

ethylenic carbinols by halogenation and dehydrohalogenation procedures. The Grignard reagents, discovered shortly afterwards, proved to be useful in this connection and in the succeeding fifty years this reaction has been found to be of an extremely general character, occurring between any compound containing a free ethynyl group and a carbonyl compound in the presence of a suitable condensing agent (cf. Johnson, "Acetylenic Compounds," Vol. I). The scope of this addition reaction, especially for large-scale applications, has been greatly extended by the efforts of Reppe and his collaborators, who have developed the use of copper and related acetylides as catalysts. This discovery was applied most successfully to the manufacture of butynediol ($HO{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH$) by the condensation of acetylene with formaldehyde, the first stage in the Reppe process for the production of butadiene.

One of the best-known synthetic uses of the ethynylcarbinols arises from their partial hydrogenation, followed by anionotropic rearrangement of the vinylcarbinols to the isomeric primary alcohols or their derivatives. The value of this reaction was early appreciated in the terpene series as is illustrated by the syntheses of linaloöl (Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 182), of farnesol and nerolidol (Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 492), and of phytol (Fischer and Löwenberg, *Annalen*, 1929, **475**, 183). Many more examples of the application of this convenient procedure are on record but some further instances from the steroid series will suffice to indicate its wide applicability. In the ethynylcarbinols prepared

$$\mathrm{Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3 + C_2H_2 \xrightarrow{NaNH_2} Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(OH){\cdot}C{\equiv}CH \xrightarrow{Na\text{-}moist\ Et_2O}}$$

$$\underset{\text{Linaloöl}}{\mathrm{Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(OH){\cdot}CH{=}CH_2}} \xrightarrow{\mathrm{Ac_2O}} \underset{\text{Geranyl acetate}}{\mathrm{Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{=}CH{\cdot}CH_2{\cdot}OAc}}$$

from the 17-ketones of the steroid series the hydroxyl group has an orientation (β) different from that of the 17-hydroxylated substances isolated from the adrenal cortex. After partial hydrogenation and rearrangement to the primary alcohol, however, a hydroxyl group with the correct orientation (α) can be introduced by hydroxylation with osmium tetroxide [*cf.* the synthesis of 17-hydroxyprogesterone (Prins and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 945) and the synthesis of Kendall's Compound *E* (Sarett, *J. Biol. Chem.*, 1946, **162**, 601)].

A major extension of the field of application of acetylenic carbinols in organic synthesis arose from the discovery of the ready anionotropic rearrangement undergone by the carbinols and glycols obtained by condensations with αβ-unsaturated carbonyl compounds (*cf. Ann. Reports*, 1944, **41**, 175). While examining the properties of the acetylenic carbinol (II) prepared from crotonaldehyde, it was found that on treatment with acids it was isomerised to the conjugated vinylacetylenic alcohol (III). The broad scope of this reaction has been clearly demonstrated, its kinetics have been studied, and the marked influence of substituent groups, which produce variations in rates of isomerisation of 10^6, is a notable feature (Braude and Jones, *J.*, 1944, 436; 1946, 122, 128). Its application in the case of the glycol (IV) from octatrienal points to its potentialities for the synthesis of conjugated polyenynes and it has found valuable use in the synthesis of vitamin A and its analogues (see Sir Ian Heilbron, *J.*, 1948, 386). Isler and his co-workers (Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911) utilised the anionotropic rearrangement of the ethynylcarbinol (V) from methyl vinyl ketone to prepare the C_6 alcohol (VI) which, by condensation with the C_{14} aldehyde (VII), furnished the glycol (VIII), ultimately converted into vitamin A.

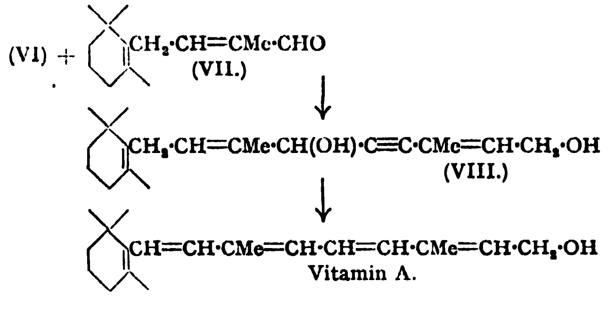
$$\text{(II.)}\quad \mathrm{CH_3{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}C{\equiv}CH \xrightarrow{acids} CH_3{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}C{\equiv}CH}\quad \text{(III.)}$$

$$\text{(IV.)}\quad \mathrm{CH_3{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH_3}$$

$$\Big\downarrow \text{acids}$$

$$\mathrm{CH_3{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH_3}$$

$$\mathrm{CH_3{\cdot}CO{\cdot}CH{=}CH_2 \longrightarrow HC{\equiv}C{\cdot}CMe(OH){\cdot}CH{=}CH_2}\ \text{(V.)} \longrightarrow \mathrm{HC{\equiv}C{\cdot}CMe{=}CH{\cdot}CH_2{\cdot}OH}\ \text{(VI.)}$$


(VI) +
CH₂·CH=CMe·CHO
CH₂·CH=CMe·CH(OH)·C≡C·CMe=CH·CH₂·OH
CH=CH·CMe=CH·CH=CH·CMe=CH·CH₂·OH

(VII.)

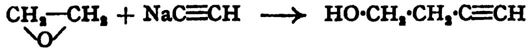
(VIII.)

Vitamin A.

The vinylcarbinols obtained by partial hydrogenation of the ethynyl compounds rearrange even more readily and in the simple case of the carbinol (IX) derived from crotonaldehyde it was shown that isomerisation occurred to give the secondary butadienylcarbinol (X) (Jones, Heilbron, McCombie, and Weedon, *J.*, 1945, 84). It appears from recent work (Nazarov and Fisher, *Chem. Abstracts*, 1949, **43**, 112) that the rapid isomerisation to the conjugated secondary carbinol is succeeded by a slow conversion into the primary sorbyl alcohol (XI).

$$\underset{\text{(IX.)}}{\mathrm{CH_3{\cdot}CH{=}CH{\cdot}CH(OH){\cdot}CH{=}CH_2}} \longrightarrow \underset{\text{(X.)}}{\mathrm{CH_3{\cdot}CH(OH){\cdot}CH{=}CH{\cdot}CH{=}CH_2}} \longrightarrow \underset{\text{(XI.)}}{\mathrm{CH_3{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH}}$$

As has already been indicated, a considerable variety of procedures can be utilised for the preparation of the normal acetylenic carbinols, *i.e.*, the αβ-acetylenic carbinols [$>C(OH){\cdot}C{\equiv}C{\cdot}$]. For the βγ-analogues (*e.g.*, XII), however, the only procedure hitherto available employs the reaction between ethylene oxides and sodium acetylide in liquid ammonia (*cf.* Kreimeier, U.S.P. 2,106,182; Macallum, U.S.P. 2,125,284). Its scope is limited by the relative inaccessibility of the oxides and by the poor yields obtained. Even with ethylene oxide it is not easy to achieve yields of more than 50% and with increasing substitution the yields fall appreciably (propylene oxide gives about 35% and *iso*butylene oxide only about 20% yields; Haynes and Jones, unpublished).



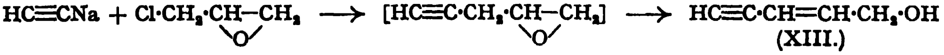
$$\underset{\diagdown O \diagup}{CH_2\text{—}CH_2} + NaC{\equiv}CH \longrightarrow HO{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH$$

(XII.)

It may be noted that it was while searching for new methods of effecting the condensation between ethylene oxide and acetylene, that the remarkable polymerisation of acetylene to *cyclo*octatetraene was revealed (Reppe, Schichting, Klager, and Topel, *Annalen*, 1948, **560**, 1). Seeking a more convenient route to the βγ-acetylenic alcohols it has now been established (Henbest, Jones, and Walls, *J.*, 1949, 2696) that the Reformatsky type of condensation, initially reported by Zeile and Meyer (*Ber.*, 1942, **75**, 356) between *cyclo*hexanone and propargyl bromide, can be extended to include aldehydes, unsaturated aldehydes, and ketones, in reactions with a variety of substituted propargyl bromides.

$$>C{=}O + BrCH_2{\cdot}C{\equiv}CH \xrightarrow{Zn} >C(OH){\cdot}CH_2{\cdot}C{\equiv}CH$$

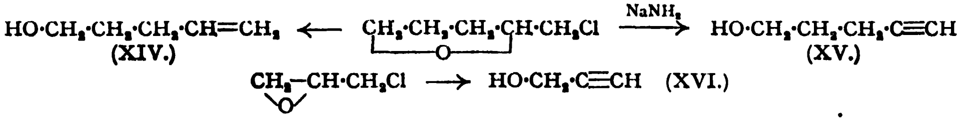
On the basis of our present knowledge it is hardly to be expected that any widely applicable methods can be devised for the preparation of γδ-acetylenic alcohols. However, two novel examples of the formation of these rather inaccessible alcohols have recently been discovered. The condensation between epichlorohydrin and sodium acetylide in liquid ammonia gave, very unexpectedly, the primary alcohol, pentenynol (XIII) in about 40% yield (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583). Unequivocal evidence indicates that the initial step in this reaction is substitution to yield the acetylenic oxide followed by rearrangement to the alcohol, rather than the alternative addition to the oxide ring and subsequent elimination of sodium chloride.



$$HC{\equiv}CNa + Cl{\cdot}CH_2{\cdot}\underset{\diagdown O \diagup}{CH\text{—}CH_2} \longrightarrow [HC{\equiv}C{\cdot}CH_2{\cdot}\underset{\diagdown O \diagup}{CH\text{—}CH_2}] \longrightarrow HC{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$$

(XIII.)

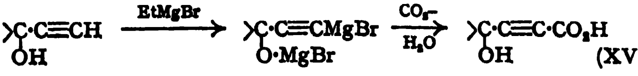
The other example originated from the work of Paul (*Bull. Soc. chim.*, 1935, **2**, 745), who described the formation of the pentenol (XIV) from tetrahydrofurfuryl chloride by treatment with sodium in an inert solvent. It has now been observed that with sodamide in liquid ammonia the corresponding pentynol (XV) is produced directly in over 70% yield. This pentynol, which has many potential synthetic uses, thus becomes one of the most easily accessible acetylenic alcohols. Propargyl alcohol (XVI) is almost certainly the major product resulting from the similar treatment of epichlorohydrin but the optimum conditions for its formation and isolation have yet to be fully elucidated (Eglinton, Jones, and Whiting, unpublished).



$$\underset{\text{(XIV.)}}{HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CH_2} \longleftarrow \underset{\llcorner\text{———}O\text{———}\lrcorner}{CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH{\cdot}CH_2Cl} \xrightarrow{NaNH_2} \underset{\text{(XV.)}}{HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH}$$

$$\underset{\diagdown O \diagup}{CH_2\text{—}CH{\cdot}CH_2Cl} \longrightarrow HO{\cdot}CH_2{\cdot}C{\equiv}CH \quad \text{(XVI.)}$$

The experiences of earlier workers on the carboxylation of ethynylcarbinols were not encouraging, but it was found that by careful attention to the reaction conditions, especially to the choice of solvent for the Grignard complex, excellent conversions into the hydroxy-acetylenic acids (XVII) could be obtained (Haynes and Jones, *J.*, 1946, 503).

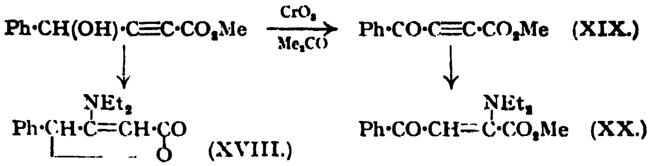


$$>\underset{OH}{C}{\cdot}C{\equiv}CH \xrightarrow{EtMgBr} >\underset{O\cdot MgBr}{C}{\cdot}C{\equiv}CMgBr \xrightarrow[H_2O]{CO_2-} >\underset{OH}{C}{\cdot}C{\equiv}C{\cdot}CO_2H$$

(XVII.)

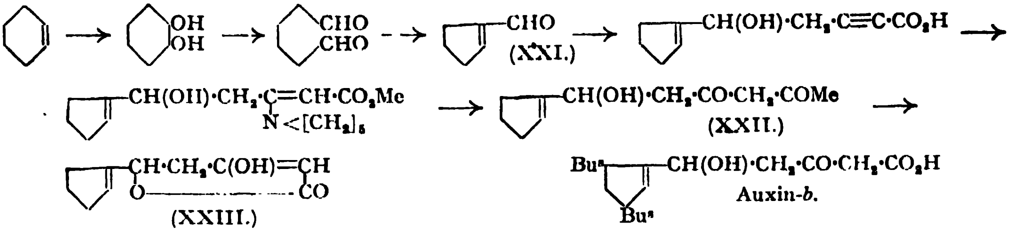
These acids have already found several synthetical applications, for example, by partial hydrogenation, syntheses of αβ-ethylenic lactones are possible (Haynes and Jones, *J.*, 1946, 954). With nucleophilic reagents, addition reactions of the esters lead to β-substituted γ-hydroxyacrylic esters which are spontaneously converted into γ-lactones (XVIII) (Jones and Whiting, *J.*, 1949, 1423). On the other hand, if the esters are first oxidised to the γ-keto-esters (XIX), a simple process, nucleophilic

addition reactions occur in the reverse direction with the formation of α-substituted β-acylacrylic esters (XX).



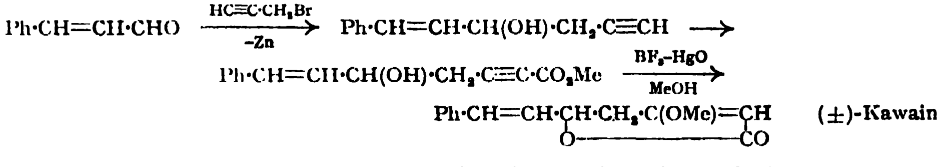
(XIX.) (XVIII.) (XX.)

By taking advantage of the nucleophilic addition reactions mentioned above, some progress has been made towards the synthesis of the plant-growth hormone, auxin-*b*, as formulated by Kögl and his collaborators (*Z. physiol. Chem.*, 1934, **225**, 215). The *cyclo*pentenealdehyde (XXI), made by a route capable of extension to the more complex aldehydes required for the final auxin synthesis, is condensed with propargyl bromide by a Reformatsky reaction, and the resulting βγ-acetylenic carbinol is carboxylated. Addition of piperidine to the acetylenic linkage of the ester, followed by mild acid hydrolysis, yields the β-keto-ester (XXII) in excellent yield.



(XXI.) (XXII.) (XXIII.) Auxin-*b*.

Hydrolysis of this ester with dilute sodium hydroxide solution, followed by acidification, leads to the lactone (XXIII), the conversion of which into the corresponding acid is at present being studied (Jones and Whiting, *J.*, 1949, 1419; Brown, Henbest, and Jones, unpublished). Mention should be made at this stage of Raphael's elegant syntheses of dihydropenicillic acid and of penicillic acid itself (*J.*, 1947, 805; 1948, 1508), both of which are based on reactions of the hydroxy-acetylenic acids. A synthesis of (±)-kawain has recently been achieved (Fowler, Henbest, and Jones, unpublished) by the application of similar reactions according to the accompanying scheme; the relationship of the synthetic material to the naturally-occurring lactone, (+)-kawain (Borsche and Peitzsch, *Ber.*, 1930, **63**, 2414) being established by the identity of their ultra-violet and infra-red spectra.



(±)-Kawain

Ethylenic linkages result from the partial hydrogenation of acetylenic bonds and, since isomerisations are unlikely to occur during hydrogenation, this procedure has distinct advantages over most others for the synthesis of ethylenic compounds containing the –CH=CH– grouping. Moreover, the partial catalytic hydrogenation of an isolated acetylenic linkage is stereo-selective, that is, it gives rise mainly to the *cis*-configuration of the resulting ethylenic bond. This almost exclusive production of the *cis*-isomer and the unequivocal position of the ethylenic bond are valuable advantages accruing from the partial hydrogenation procedure; moreover, in the majority of the naturally occurring unsaturated fatty acids, the *cis*-orientation is found. It is not surprising therefore, to find several examples in which this procedure is utilised. It should be noted that transformation into the *cis*-form is not absolutely quantitative: some complete hydrogenation occurs and traces of the *trans*-isomer may be present. However, the isolation of pure *cis*-forms is relatively simple when crystallisable materials are being employed.

In the synthesis of unsaturated lactones already referred to, lactonisation is possible only as a result of the *cis*-orientation of the double bond; in this case any *trans*-acid is eliminated on distillation. Lauer and Gensler (*J. Amer. Chem. Soc.*, 1945, 67, 1171) have achieved the synthesis of the *cis*-form of the plant-growth hormone, traumatic acid, by partial hydrogenation

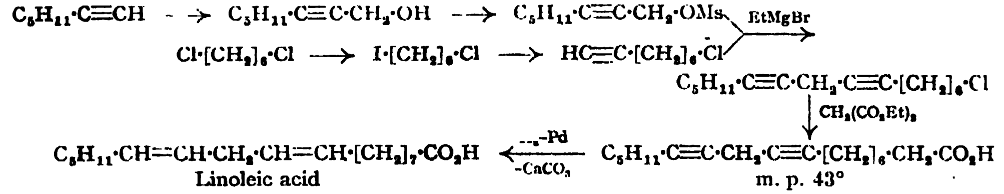
of the corresponding acetylenic dicarboxylic acid. The synthesis of *cis*- and *trans*-octadec-11-enoic acids (Akmad, Bumpas, and Strong, *J. Amer. Chem. Soc.*, 1948, **70**, 3391, *cf.* 1699) illustrates

$$\mathrm{HC{\equiv}C{\cdot}[CH_2]_8{\cdot}CO_2H \xrightarrow[+\,CO_2]{Na\ salt} HO_2C{\cdot}C{\equiv}C{\cdot}[CH_2]_8{\cdot}CO_2H \xrightarrow[Ni]{H_2-}}$$
$$\mathrm{HO_2C{\cdot}CH{=}CH{\cdot}[CH_2]_8{\cdot}CO_2H} \quad \textit{cis}\text{-Traumatic acid.}$$

clearly the potentialities for syntheses in the fatty acid series. Alkylation of oct-1-yne with a polymethylene chloride iodide leads to the chloro-alkyne and treatment of this with sodium cyanide suffices to provide the required carbon skeleton. Partial hydrogenation produces the *cis*-acid, which, on heating with selenium gives the *trans*-isomer. Mention should also be made

$$\mathrm{C_6H_{13}{\cdot}C{\equiv}CH + I{\cdot}[CH_2]_9{\cdot}Cl \xrightarrow[NH_3]{Na-liq.} C_6H_{13}{\cdot}C{\equiv}C{\cdot}C{\cdot}[CH_2]_9{\cdot}Cl \xrightarrow[hydrol.]{NaCN\ and}}$$
$$\mathrm{C_6H_{13}{\cdot}C{\equiv}C{\cdot}[CH_2]_9{\cdot}CO_2H \xrightarrow{Ni-H_2} (\textit{cis-})C_6H_{13}{\cdot}CH{=}CH{\cdot}[CH_2]_9{\cdot}CO_2H \xrightarrow{Se,\ heat}} \textit{trans-}\ \text{(vaccenic acid)}$$

of the syntheses of geometrical isomerides of the naturally occurring insecticide, pellitorine, and the homologous herculin (Raphael and Sondheimer, *Nature*, 1949, **164**, 707), and of syntheses of alkenylphenols related to the constituents of cashew nut shell liquid and urushiol, the vesicant principle in poison ivy (Sletzinger and Dawson, *J. Org. Chem.*, 1949, **14**, 849; Wasserman and Dawson, *ibid.*, 1943, **8**, 73). An interesting extension of these methods is to be found in the recent work of Raphael and Sondheimer (*Nature*, in the press) on the synthesis of linoleic acid, presumably in the *di-cis*-form. The final product has as yet been obtained only in small



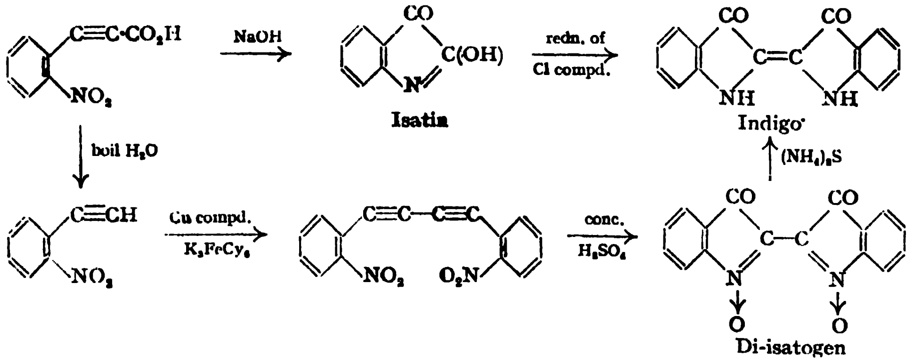
$$\mathrm{C_5H_{11}{\cdot}C{\equiv}CH \rightarrow C_5H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH \longrightarrow C_5H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OMs}$$
$$\mathrm{Cl{\cdot}[CH_2]_6{\cdot}Cl \longrightarrow I{\cdot}[CH_2]_6{\cdot}Cl \longrightarrow HC{\equiv}C{\cdot}[CH_2]_6{\cdot}Cl}$$
$$\xrightarrow{\mathrm{EtMgBr}} \mathrm{C_5H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}[CH_2]_6{\cdot}Cl} \xrightarrow{\mathrm{CH_2(CO_2Et)_2}}$$
$$\mathrm{C_5H_{11}{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}[CH_2]_6{\cdot}CH_2{\cdot}CO_2H}\ \text{m. p. }43^\circ$$
$$\mathrm{C_5H_{11}{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[CH_2]_7{\cdot}CO_2H \xleftarrow[-CaCO_3]{H_2-Pd}}$$

quantity but it gave a tetrabromide with the correct melting point. In view of the freedom from double-bond migration, procedures of this type may well prove to be particularly suitable for the synthesis of the rather unstable acids of the drying-oil type.

In 1870, Glaser (*Annalen*, **154**, 159) made the surprising observation that, when the copper derivative of phenylacetylene was oxidised with air in ammoniacal alcoholic solution, a smooth

$$\mathrm{Ph{\cdot}C{\equiv}CH \longrightarrow Ph{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}Ph}$$

coupling reaction occurred yielding diphenyldiacetylene. This work was extended by Baeyer in connection with his classical studies in the indigo series. He effected the coupling of the



copper derivative of *o*-nitrophenylacetylene with potassium ferricyanide and converted the di(nitrophenyl)diacetylene with sulphuric acid into di-isatogen and thence produced indigo by reduction with ammonium sulphide. These experiments provided the first real evidence of the nature of the carbon skeleton of indigo (Baeyer, *Ber.*, 1880, **13**, 2254; 1882, **15**, 50).

The coupling reaction has been extensively studied and it has recently been shown, contrary to the experiences of earlier workers, that the coupling of ethynylcarbinols by the convenient procedure of aerial oxidation in the presence of cuprous ammonium chloride is a general reaction, applicable to carbinols of various types (Bowden, Heilbron, Jones, and Sargent, *J.*, 1947, 1579). Furthermore, the function of the cuprous salt appears to be largely catalytic and considerably less than one equivalent can be employed.

The application of this oxidative coupling in the case of pentenynol (XXIV) to give the glycol (XXV) in 70% yield (Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586) gives an indication of the scope of the method. Mixed coupling reactions cannot easily be effected in this way but it is worthy of note that Baeyer and Landsberg (*Ber.*, 1882, **15**, 57) obtained a good yield of *o*-nitrodiphenyldiacetylene by treating a mixture of phenylacetylene and nitrophenylacetylene with ammoniacal cuprous chloride and oxidising the mixed copper salts with potassium ferricyanide. Such mixed coupling reactions are better carried out, however, by interaction of acetylenic Grignard reagents with iodoacetylenes (Grignard and Perichon, *Ann. Chim.*, 1926, **5**, 5; Horn and Weedon, forthcoming communication).

(XXIV.) $2HC\equiv C\cdot CH=CH\cdot CH_2\cdot OH \longrightarrow HO\cdot CH_2\cdot CH=CH\cdot C\equiv C\cdot C\equiv C\cdot CH=CH\cdot CH_2\cdot OH$ (XXV.)

By oxidation of secondary ethynylcarbinols in acetone solution with chromic acid, the highly reactive ethynyl ketones (*e.g.*, XXVI) are readily prepared (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39). These substances undergo with notable facility a variety of addition reactions, and those with amines and other nucleophilic reagents, and with dienes, have been studied in some detail (Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45; Bowden and Jones, *J.*, 1946, 52; Bowden, Braude, and Jones, *J.*, 1946, 953). Application of the selective oxidation procedure to primary acetylenic alcohols yields the corresponding acids, and even the unsaturated glycol (XXV) can be oxidised smoothly to the dicarboxylic acid (XXVII) (Heilbron, Jones, and Sondheimer, *J.*, 1949, 604).

$$Ph\cdot CH(OH)\cdot C\equiv CH \longrightarrow Ph\cdot CO\cdot C\equiv CH \quad \text{(XXVI.)}$$

$$\text{(XXV)} \longrightarrow HO_2C\cdot CH=CH\cdot C\equiv C\cdot C\equiv C\cdot CH=CH\cdot CO_2H \quad \text{(XXVII.)}$$

Kuhn and Wallenfells (*Ber.*, 1938, **71**, 1510, 1889) achieved conspicuous success in the synthesis of polyenes and cumulenes *via* acetylenic glycols. From the 1 : 4- and 1 : 6-glycols, obtained by condensation of carbonyl compounds with acetylene and diacetylene, partial hydrogenation with palladium catalysts, followed by treatment with phosphorus di-iodide or chromous or vanadous chlorides, gave good yields of diphenylpolyenes (*e.g.*, XXVIII). On the other hand, direct reduction of the glycols with chromous chloride in the presence of hydrogen chloride yielded cumulenes, the scarlet tetraphenylhexapentaene (XXIX) being formed from the diacetylenic glycol from benzophenone in 90% yield.

$$Ph\cdot CH=CH\cdot CH(OH)\cdot C\equiv C\cdot CH(OH)\cdot CH=CHPh \xrightarrow{Pd-H_2}$$

$$Ph\cdot CH=CH\cdot CH(OH)\cdot CH=CH\cdot CH(OH)\cdot CH=CHPh \longrightarrow Ph\cdot CH=CH\cdot CH=CH\cdot CH=CH\cdot CH=CHPh \quad \text{(XXVIII.)}$$

$$Ph_2C(OH)\cdot C\equiv C\cdot C\equiv C\cdot C(OH)Ph_2 \longrightarrow Ph_2C=C=C=C=C=CPh_2 \quad \text{(XXIX.)}$$

Not unrelated to these studies are some investigations carried out during the past year on the preparation of the conjugated poly-ynes, compounds containing a series of conjugated acetylenic linkages. The diacetylenes or di-ynes of this type are of course well known, being readily available by the coupling reaction already described. As long ago as 1885, Baeyer (*Ber.*, **18**, 674, 2269) conceived the idea of making a conjugated tetra-acetylenic compound by the coupling of diacetylenecarboxylic acid, $HC\equiv C\cdot C\equiv C\cdot CO_2H$, but the product proved to be extraordinarily unstable although on reduction with sodium amalgam he did obtain a small amount of what might have been sebacic acid.

In seeking general methods we directed our attention to the observation that 1 : 4-dichlorobut-2-yne (XXX), prepared from the easily accessible butynediol with thionyl chloride, yields diacetylene on treatment with alkaline reagents (cf. Keyssner and Eichler, G.P. 750,637; Johnson, *J.*, 1946, 1009, 1014). It has now been found (Armitage, Jones, and Whiting, unpublished) that, when this process is carried out with sodamide in liquid ammonia, either the mono- or the di-sodio-derivative of diacetylene can be obtained at will, practically instantaneously and in quantitative yields. The ready production of the monosodio-derivative is particularly important since by straightforward substitution reactions, carried out subsequently in the liquid ammonia medium, mono-substituted diacetylenes (XXXI) can easily be made. Already we have observed that these substances can be coupled by the standard methods to yield the conjugated tetra-acetylenes or tetra-ynes (XXXII).

$$\underset{\text{(XXX.)}}{\mathrm{ClCH_2{\cdot}C{\equiv}C{\cdot}CH_2Cl}} \xrightarrow[\text{liq. NH}_3]{\mathrm{NaNH_2}} \mathrm{NaC{\equiv}C{\cdot}C{\equiv}CH} \xrightarrow{\text{RHal}} \underset{\text{(XXXI.)}}{\mathrm{R{\cdot}C{\equiv}C{\cdot}C{\equiv}CH}} \xrightarrow{\mathrm{EtMgBr{-}I_2}} \underset{\text{(XXXII.)}}{\mathrm{R{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}R}}$$

If the disodio-derivative, in the liquid ammonia in which it is formed, is treated with formaldehyde, then hexadiynediol (XXXIII) is produced in almost 90% yield. This can be

$$\mathrm{NaC{\equiv}C{\cdot}C{\equiv}CNa} \xrightarrow{\mathrm{CH_2O}} \underset{\text{(XXXIII.)}}{\mathrm{HO{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH}} \xrightarrow[\mathrm{C_5H_5N}]{\mathrm{SOCl_2}-}$$

$$\mathrm{ClCH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2Cl} \xrightarrow[\text{liq. NH}_3]{\mathrm{NaNH_2}} \mathrm{NaC{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}CNa} \xrightarrow{\text{MeI}} \mathrm{Me{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}CMe}$$

converted into the dichloride, and by repetition of the sodamide treatment the sodio-derivatives of triacetylene are obtained, and its mono- and di-alkyl derivatives and other condensation products thus become available.

It is not possible at this stage to give more than a brief description of the properties of these novel substances, the parents of which are the polyacetylene hydrocarbons, C_nH_2. Considerable differences have been observed between individual members and, although in general they appear to be rather unstable under normal conditions, in nitrogen or in a vacuum at −70° they can be kept for reasonable periods. Dimethyltriacetylene (1 : 6-dimethylhexatriyne) crystallises well and has m. p. 128°, and dimethyltetra-acetylene (1 : 8-dimethyloctatetrayne), which is also beautifully crystalline, decomposes when heated above about 80°. The ultra-violet light absorption properties of the tetra-acetylenes have revealed some unexpected features, especially the remarkably high intensity of the absorption in the 2200—2500-A. region. The intensities, ε = about 270,000, which have been observed in several cases, are amongst the highest ever recorded. Now that methods of synthesis have been developed, it is hoped to examine the physical properties of a wide range of substances of this polyacetylene series, since the enforced linearity of the conjugated poly-yne chain might be expected to endow these predominantly carbon-containing molecules with exceptional properties.

Acetylene has frequently been employed in synthetic work mainly as a convenient and reactive unit for building up the required carbon skeletons. The scope for the use of acetylenic compounds in synthesis is, however, by no means restricted to this purpose, and in many of the cases already discussed due advantage has been taken of the well-known and unique addition reactions of the triple bond in order subsequently to introduce functional groups. No attempt can be made here to summarise these addition reactions, but some recently discovered procedures which break new ground merit special attention.

The first of these concerns the conversion of ethynyl compounds into aldehydes. It has long been known that methyl ketones or their derivatives result from the catalysed hydration of compounds containing an ethynyl group; attempts have been made to obtain aldehydes by reversing the direction of hydration but such successes as have been claimed have been shown

$$\mathrm{R{\cdot}CH_2{\cdot}CHO} \dashleftarrow \mathrm{R{\cdot}C{\equiv}CH} \longrightarrow \mathrm{R{\cdot}CO{\cdot}CH_3}$$

to be largely ill-founded (for summary, cf. Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244). It has now been found that when thiolacetic acid reacts with monosubstituted acetylenes, under the influence of organic peroxides or irradiation with ultra-violet light, mono- and di-adducts are produced by " abnormal " addition reactions. The mono-adducts on treatment with the usual carbonyl reagents are converted smoothly into derivatives of the corresponding aldehydes, while,

$$\begin{tikzcd}
 & \mathrm{Bu{\cdot}CH{=}CH{\cdot}SAc} \arrow[r, "\mathrm{NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2}"] & \mathrm{[Bu{\cdot}CH{=}CH{\cdot}SH]} \arrow[r] & \mathrm{Bu{\cdot}CH_2{\cdot}CH{=}N{\cdot}NH{\cdot}CO{\cdot}NH_2} \arrow[dd] \\
\mathrm{Bu{\cdot}C{\equiv}CH} \arrow[ur] \arrow[dr] & + & & \\
 & \mathrm{Bu{\cdot}CH(SAc){\cdot}CH_2{\cdot}SAc} \arrow[r] & \mathrm{Bu{\cdot}CH(SH){\cdot}CH_2{\cdot}SH} & \mathrm{Bu{\cdot}CH_2{\cdot}CHO}
\end{tikzcd}$$

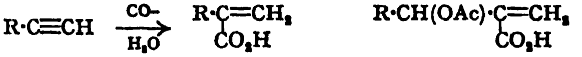
under rather more acidic conditions, the di-adducts yield 1 : 2-dithiols (Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619 ; cf. Behringer, *Annalen*, 1949, **564**, 219).

Another elegant method of obtaining aldehydes *via* acetylenic compounds has been described by Arens and Van Dorp (*Nature*, 1947, **160**, 189; *Rec. Trav. chim.*, 1948, **67**, 973) in connection with their important synthetic work in the vitamin A series. These authors found that the carbinols arising from condensation of ethoxyacetylene with carbonyl compounds gave, after partial hydrogenation, ethylenic carbinols convertible by mild treatment with dilute acids into

$$>C{=}O \longrightarrow >C(OH){\cdot}C{\equiv}C{\cdot}OEt \xrightarrow{H_2} >C(OH){\cdot}CH{=}CH{\cdot}OEt \xrightarrow{\text{acids}} >C{=}CH{\cdot}CHO$$

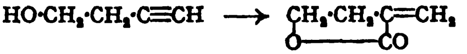
αβ-unsaturated aldehydes. The last stage in this procedure is analogous to the behaviour of certain β-chlorovinylcarbinols under similar conditions (Jones and Weedon, *J.*, 1946, 937).

Finally, the discovery by Reppe and his collaborators (B.I.O.S. Final Reports Nos. 266, 355, and 358; see also *Experientia*, 1949, **5**, 93) of a method of effecting the combination of acetylenic compounds and carbon monoxide provides an outstanding additional rôle to the already extensive repertoire of the acetylenic bond in synthetic operations. Using nickel carbonyl, either stoicheiometrically or, together with carbon monoxide, as a catalyst, in reactions either with acetylene itself or with simple acetylenic hydrocarbons, Reppe succeeded in obtaining acrylic acid and related substances. This novel reaction thus leads to syntheses of branched-chain compounds by addition to the triple bond, a possibility realised hitherto only in a few instances such as the application of the Michael reaction to αβ-acetylenic carbonyl compounds (*e.g.*, Dey, *J.*, 1937, 1057). Much careful study has been necessary in order to find suitable conditions for the extension of this reaction to acetylenic carbinols but, by employing the acetates of the carbinols in reactions with nickel carbonyl in alcohol–acetic acid media, reasonable conversions into analogues (XXXIV) of acrylic acid have been achieved. From the βγ-acetylenic carbinols, the hitherto practically inaccessible methylenebutyrolactone (XXXV), a naturally-occurring antibiotic (Cavallito and Haskell, *J. Amer. Chem. Soc.*, 1946, **68**, 2332), has been synthesised in this way (Jones, Shen, and Whiting, *J.*, in the press).



$$R{\cdot}C{\equiv}CH \xrightarrow[H_2O]{CO-} R{\cdot}C(CO_2H){=}CH_2 \qquad R{\cdot}CH(OAc){\cdot}C(CO_2H){=}CH_2$$

(XXXIV.)



$$HO{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH \longrightarrow \underset{O\text{———}CO}{CH_2{\cdot}CH_2{\cdot}C{=}CH_2}$$

(XXXV.)

It is usual at this stage, when so much collaborative work has been described, for some tribute to be paid to those who, by their efforts, have contributed to the development of the subject. Although my remarks must, of necessity, be brief, I do not pay this tribute in any perfunctory spirit, but rather with a deep and sincere feeling of gratitude for the wholehearted co-operation and assistance which it has been my good fortune to receive. It is a source of much pleasure to note that several of our former co-workers are actively engaged in exploring and exploiting new territories in the vast realm which is acetylene chemistry.

To you, Mr. President, in your rôle as teacher, colleague, and friend, and to our many collaborators, both past and present, to whom most of the credit is due, I offer my warmest thanks.

OBITUARY NOTICE.

ALEXANDER SCOTT.

1853—1947.

[Abridged, by permission, from the Notice by the late Sir Robert Robertson in *Obituary Notices of Fellows of the Royal Society*, 1948, **6**, 251—262.]

On 10 March 1947, at the great age of ninety-three, Dr. Alexander Scott, inorganic chemist, died at Ringwood, Hampshire. He was born in the county town of Selkirk on 28 December 1853, the son of Alexander Scott and the eldest of a family of four sons and four daughters, some of whom are now living.

The family appears to have migrated from the Scott Border country, for there are records of forebears being settled in Fife, in Kilconquhar or its neighbourhood, in the middle of the eighteenth century, evidently as farmers.

It was thus a return to the Scott country that the father of the subject of this Notice made when he was appointed Rector of Selkirk Academy in 1851, a post he held for thirty three years. He was also Kirk Session Clerk for twenty-eight years and an Elder for nine. To a testimonial in 1883, one hundred and sixty-five of his former pupils put their names and among these is Andrew Lang, who was Selkirk-born. It is however as a botanist that the Rector had the greatest influence over his son, for he was a field botanist of repute, identifying wild plants scientifically by the Flora and making excursions after the rarer kinds. Not only had this a profound effect on the son as is shown by his love of flowers, by his choice of botanists as friends and by his selection of plants in his London garden, but in the opinion of the writer, who has had a similar fortunate experience, it was an early introduction to practice in scientific method.

In those days it was the custom to send boys to the University at an age which seems to us somewhat immature. Accordingly, young Scott matriculated at Edinburgh University in November 1868 at the age of fifteen. At first he had the idea of becoming an engineer, and towards this end studied under Tait and Fleeming Jenkin. Nor was botany neglected, for he attended the lectures of Balfour who had brought from the school of Sachs physiological botany, a supplement to the field botany in which he had been hitherto interested. These studies were, however, soon subordinated to chemistry when he came under the influence of Crum Brown and of Dewar. Crum Brown not only devoted himself to those questions of structural chemistry with which we associate him, but ran large classes of over a hundred. It was a source of pleasure to Scott that in such a class he had the distinction of being Senior Medallist. In 1876 he graduated B.Sc. in Experimental Philosophy, his Doctorate following in 1884 with a thesis " On the atomic weight of manganese." During this time, as also later, he was noted for his phenomenal knowledge of the materials of inorganic chemistry.

From 1872 to 1875 Dewar was lecturer at the Dick Veterinary College and Scott was his student assistant.

In 1875 Dewar was elected Jacksonian Professor of Natural Experimental Philosophy at Cambridge, whither Scott followed him in the same year, having been appointed assistant to the Jacksonian Professor. Here he lectured on physical and organic chemistry and supervised advanced students engaged in research. In 1876 he obtained a Clothworkers' Exhibition in physical science, and in 1878 a Foundation Scholarship in natural science at Trinity College. In 1879 he took his B.A. with first-class Honours in natural science, and graduated M.A. in 1882. He also examined for Tripos and other examinations.

Influenced by Dr. Fearon, the headmaster of Durham School, in June 1884, Scott undertook the entire management of the science teaching in Durham School in a new laboratory erected by the Governors under his supervision. He was further induced to make the change as opportunity of time for original research was offered. Later, in a new chemical and metallurgical laboratory erected and equipped under his direction at Middlesbrough, by the Trustees of the High School, he lectured to large classes—with great acceptance according to Sir Hugh Bell. Scott welcomed this opportunity of developing scientific teaching in the North of England, for, as he says in his first Presidential Address to the Chemical Society (1916), educational matters always interested him profoundly.

It was while here that Scott found the teaching of science in poor case, being handicapped by science masters either ill-trained or having to subordinate their efforts to preparing their pupils for answering the highly specialised questions of scholarship examinations. In the same

Alexander Scott

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[*To face p.* 762.

Presidential Address, the opportunity of successful careers for science students is compared with the rewards open to classical or mathematical students, and an appeal is made for a change of outlook.

Scott while at Durham must have led a strenuous life, for not only had he the supervision of the teaching of science at Durham and Middlesbrough schools, but he was busy at his experimental work, especially with his apparatus for determining the combining volumes of hydrogen and oxygen, towards which he received a grant from this Society, but in addition he found time to write a textbook, "Introduction to Chemical Theory," A. and C. Black, 1891, which ran into a second edition.

In 1891 Scott returned to Cambridge as Demonstrator to the Jacksonian Professor (Dewar) and took up the threads of his experimental work and his tutorial activities. As before, the main topic of his research was connected with the determination of accurate atomic weights, and between 1891 and 1896 he presented several papers and wrote reviews of the subject to the scientific press.

In 1877 Dewar had become Fullerian Professor of Chemistry at the Royal Institution. This Institution took over the Davy-Faraday Research Laboratory in 1896 by Deed of Trust from Dr. Ludwig Mond who had munificently bought the next-door premises, furnished them as laboratories and had put £62,000 aside for running expenses. The Laboratory was opened with much ceremony on 22 December 1896 by H.R.H. the Prince of Wales. It was designed to afford opportunities for skilled workers who had the wish and time to devote to the solution of important problems. All laboratory facilities but no emoluments were provided for the workers. Professor Dewar and the third Lord Rayleigh were appointed Directors, and Dr. Alexander Scott Superintendent of the Laboratory. Here Scott worked for fifteen years on the determination of the atomic weights of various elements and methods for the preparation of substances in a state of high purity, but his advice was frequently asked by the workers in the Laboratory, who included Horace T. Brown, H. Debus, A. Liversidge, A. Mallock, Hugo Müller, Joseph Petavel, Charles E. S. Phillips, P. C. Ray, W. J. Russell, G. Senter, and Henry T. Tizard. With these his relations were very amicable and he held the respect of the staff. As one of the workers of that time has said, Scott had a kindly friendliness to the sincere worker. He was intolerant of slip-shod work.

This went on till 1910 when it was decided by the Managers to terminate the office of Superintendent in 1911. This led to much acrimony between Scott and Dewar, as might be expected between two personalities of such individualistic and independent character.

In 1898 Scott was elected into the Royal Society.

Scott now worked in his own laboratory at Upper Hamilton Terrace and devoted much time to the affairs of the Chemical Society. After having been two years on the Council (1897—1899) he held the post of Secretary until 1904 when he became Treasurer and held this office until his Presidency (1915—1917). More systematic arrangements for the conduct of its business were made by Scott, and under his leadership the first steps were taken which led to the formation and incorporation of the Association of British Chemical Manufacturers, a body which has done much to secure a prosperous chemical industry and had itself provided assistance to the Chemical Society.

During this period Scott delivered two Presidential Addresses to the Chemical Society : the one (1916) containing a sketch of the history of the Society, Scott's views on research and his strictures on the outlets for chemists, referred to above, and the other (1917) dealing with the atomic theory and Prout's hypothesis.

A new interest was aroused when, in 1919, at the request of the Department of Scientific and Industrial Research, Scott conducted an inquiry into the condition of objects at the British Museum alleged to have suffered deterioration by storage in London's Underground during the 1914—1918 war. A small laboratory was established at the Museum on his recommendation, sanctioned by H.M. Treasury on the condition of its being a "purely temporary experiment to come to an end in three years." Here, under his supervision, a scientific study was made of ancient materials and their reactions to various environments, and methods of preservation and restoration were worked out and in due course published. How successful was the work done may be judged by the subsequent development of the laboratory idea in museums in general, by the eventual incorporation of the original laboratory as a separate department of the British Museum (recommendation of the Royal Commission on Museums) and by the views of the parent Department expressed at the time of transfer recording cordial appreciation of the distinguished service of Dr. Scott, "service which has enhanced very considerably the value of our National Collections and works of art."

He retired in 1938, aged 85, mentally as alert as ever and able to maintain the keenest interest in science and in museum work to the very end. He was beloved by his staff at the Museum, and for them will remain a great tradition, a symbol of the dignity of science and of mental vigour and integrity.

SCIENTIFIC WORK.

Attainment of the highest possible accuracy in the determination of the atomic weights of elements was the method, but the philosophical inquiry underlying Scott's work was as to whether Prout's hypothesis was true in fact.

In Dalton's Atomic Theory it is postulated that all the atoms of an element are similar and equal in atomic weight. For many years this was fully accepted by chemists, with one exception, that of Crookes who, in 1886, suggested the idea of the heterogeneity of atoms, a conception at that time and for many years after considered as highly speculative, but which was nevertheless true, for many years later Aston showed that atoms are accompanied by other atoms of similar chemical properties but of slightly different weight called isotopes, whose relative abundance settles the atomic weight as determined by analysis.

Founding his speculation on Dalton, Prout, an English chemist and physician, sent in to the *Annals of Philosophy* in 1815 and 1817, papers in which, with the values then available, he calculated that the weights of a number of elements were multiples of that of hydrogen; this he considered the πρώτη ὕλη of the Greek philosophers. The validity of this hypothesis was a matter of contention among chemists for a hundred years.

The obvious course was to ascertain if it was true in fact, and the quest proved a very potent stimulus to inquiry, especially demanding the most careful determination of atomic weights. To this end chemists applied themselves, striving after more and more accuracy by using greater and greater precautions. Various compromises were suggested, for example, halving the unit on account of the uncomfortable value of 35½ for chlorine, and even quartering it. Dumas, in 1842, by a method used earlier by Berzelius and Dulong, that of passing a stream of hydrogen over a weighed quantity of heated copper oxide and weighing the water produced, got a result showing that 2 parts of hydrogen are combined with 15·96 parts of oxygen, but Dumas, on the basis of Prout's hypothesis, assumed the ratio 2 : 16.

The chemists were divided as to the validity of Prout's hypothesis. When, in 1860, Stas, the superb experimenter, began his researches, he undertook them as he said, with " an absolute belief in the exactness of the principle of Prout," but in a few years, as a result of his own work, he took the view " that the hypothesis of Prout is a pure illusion."

In 1880, Mallet stated that out of eighteen elements, ten approximate to integers within a range of 0·1 unit, and remarked that " not only is Prout's Law not as yet absolutely overturned, but a heavy increasing weight of probability in its favour or in favour of some modification of it exists and demands consideration."

It was thus at a time when unequivocal values were required for atomic weights that Scott started, at first in Cambridge with Dewar, then extramurally by himself at Durham, then again alone at Cambridge and finally at the Royal Institution, to provide accurate atomic weights, always having in mind the need to test Prout's hypothesis.

Atomic Weight of Potassium and Sodium.—During 1875—1884 published papers are in the names of Dewar and Scott, and in the first of these were determinations of the vapour densities of potassium and sodium (1879), as a clue to their atomic weights. The Victor Meyer displacement method was used, and in the first instance the metals were vaporised in a heated iron pot. As difficulties arose from the action of the vapour on iron, this was then replaced by a platinum vessel in spite of the " terrible waste " of the metal. It is concluded that in the state of vapour potassium and sodium are monatomic, but this method does not, of course, provide precise atomic weights.

Atomic Weight of Manganese.—Determination of the atomic weight of manganese follows (1881), values having been reported varying from 54 to 55. As objections could be seen to the reagents used by previous workers, a new one was chosen—silver permanganate, a substance having the advantages of being obtained pure by crystallisation and also of not being hygroscopic. The first experiments, in which the salt was decomposed with loss of oxygen, gave discrepant results, but good ones were got by titrating the silver by an acid solution of potassium bromide, all the precautions laid down by Stas for this kind of work being observed. The mean of eight concordant experiments was 55·038, taking oxygen at 16 and Stas's value for silver 107·93. This is very near the most recent value adopted by the International Committee on Atomic Weights, 54·93 (Silver 107·88).

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1904. The combining volumes of carbon monoxide and oxygen. *Proc.*, p. 85.
1904. The decomposition of oxalates by heat. *Proc.*, p. 156.
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1905. Note on the atomic weight of nitrogen. *Proc.*, p. 309.
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1916. Presidential address to Chemical Society. *J.*, **109**, 338.
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152. *The Effect of Varying the Cation in Some Organic Reactions requiring an Alkaline Medium.*

By O. L. Brady and J. Jakobovits.

In the methylation of lactam–lactim tautomerides in alkaline media with methyl sulphate the nature on the alkali appreciably alters the ratio of *O*- to *N*-methylation, the most marked difference being between sodium hydroxide and a tetra-alkylammonium hydroxide.

In the Reimer–Tiemann reaction, with sodium hydroxide the ratio of *ortho*- to *para*-substitution is approximately 2 : 1, with cæsium hydroxide 1 : 1, and with methyltriethylammonium hydroxide 1 : 2.

Kinetic studies have been made of the hydrolysis of a number of esters. With methyl sulphate, in 0·1N-alkali in aqueous methyl alcohol, change of alkali has little effect; but with ethyl sulphate in 1N-alkali in aqueous methyl alcohol, passing from sodium hydroxide to methyltriethylammonium hydroxide approximately doubles the rate constant.

The hydrolyses of alkali alkyl phthalates $C_6H_4(CO_2M)CO_2R$, where M is Na or $NMeEt_3$, with the corresponding alkali hydroxide MOH show no difference in rate constants in aqueous solution, but in aqueous methyl alcohol the hydrolysis when M = Na has a rate constant about ten times that found when $M = NMeEt_3$.

An explanation of these results is suggested depending on formation of co-ordination complexes.

It has long been known that use of sodium and silver salts often gives different products in the alkylation of compounds capable of tautomerism, *e.g.*, in the methylation of isatin, cyanides, and nitrites, but the fact that these reactions are often, of necessity, carried out in hetereogenous media, with the solid salt, has deterred speculation on the causes of the different directions in which they proceed. A classical example of the effect of a change of metal within the same group of the Periodic Table is the Kolbe–Schmidt reaction, in which sodium phenoxide heated under pressure with carbon dioxide gives sodium salicylate but potassium phenoxide under similar conditions gives a large proportion of potassium *p*-hydroxybenzoate (Kolbe, *J. pr. Chem.*, 1874, [ii], **10**, 95; Brunner, *Annalen*, 1907, **351**, 326; Tijmstra Bz, *Ber.*, 1905, **38**, 1375; Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3029). Neogi (*J.*, 1906, **89**, 1900; 1914, **105**, 2371; 1916, **109**, 701) found that when a sodium alkyl sulphate was fused with sodium nitrite the ratio of the yields of alkyl nitrite and nitroparaffin was 0·36 : 1, whereas it was 1·9 : 1 when the potassium salts were used. Here again solid salts were employed.

Graebe (*Annalen*, 1905, **340**, 244) noted that dry potassium benzoate gave, with methyl sulphate, a better yield of methyl benzoate than was obtained from sodium benzoate, and that potassium benzoate was methylated by potassium methyl sulphate more readily than by sodium methyl sulphate. Ullmann (*Ber.*, 1900, **33**, 2774; *Annalen*, 1902, **327**, 104) found that phenols were methylated equally well in sodium hydroxide or potassium hydroxide solution or in the form of the solid sodium or potassium phenoxide. Klemenc (*Monatsh.*, 1917, **38**, 553) found that, in the methylation with methyl sulphate of quinol and resorcinol in aqueous alkali, potassium hydroxide gave a much smaller yield than sodium hydroxide, suggested that the former hydrolysed methyl sulphate faster than did the latter, and confirmed this by measuring the rate constants of the heterogeneous hydrolysis of methyl sulphate by N-alkali at 11°, finding $k_{\text{KOH}}/k_{\text{NaOH}} = 1{\cdot}25$.

These reactions were carried out in a heterogeneous medium and might be accounted for by different rates of diffusion of methyl sulphate into the alkaline solutions, or by greater solubility of methyl sulphate in potassium hydroxide solution, as well as by a specific effect of the cation.

Walden and Centnerszwer (*Z. Elektrochem.*, 1909, **15**, 310) however, measured the rate constants of the reaction

$$\text{Me}_2\text{SO}_4 + \text{MCNS} = \text{MeCNS} + \text{MeMSO}_4$$

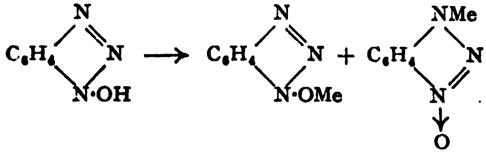
where M = Na or K, in homogeneous methyl alcoholic solution and found for 0·5N-solution $k_{\text{K}}/k_{\text{Na}} = 1{\cdot}14$, for 0·25N-solution 1·06, and for 0·125N-solution 1·34.

Other reactions are recorded in which the rate constants with different alkalis appear to be unchanged; for example, Meyer (*Z. anorg. Chem.*, 1921, **115**, 212) could not detect an appreciable difference in the rate constants for the hydrolysis of ethyl acetate by the hydroxides of lithium, sodium, potassium, rubidium, and cæsium in approximately N./10-solution. It will be shown later, however, that this is too low a concentration to show an effect of variation in the cation.

Reimer and Tiemann (*Ber.*, 1876, **9**, 824) state that, contrary to experience in the Kolbe–Schmidt reaction, in their synthesis of hydroxy-aldehydes the proportion of *ortho*- and *para*-derivatives is unaffected by changing from sodium hydroxide to potassium hydroxide; and Walden (*Ber.*, 1899, **32**, 1833), for the hydrolysis of α-chlorosuccinic acid by 0·4N-alkali, found that the rotation of the malic acid obtained differed considerably according to the alkali used (LiOH +100°; NaOH +150°; KOH +425°; RbOH +440°; aq. NH_3 +460°).

The effect of varying the cation has now been investigated further, first, on the products of methylation of tautomeric compounds, secondly on the proportion of *ortho*- : *para*-substitution in the Reimer–Tiemann reaction, and thirdly on the hydrolysis of esters.

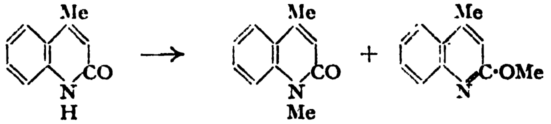
In studying methylation it was necessary to choose a compound, stable to alkali, which gave reasonable amounts of the isomeric methyl derivatives. Such was found in 1-hydroxybenztriazole which with methyl sulphate in 2N-alkli gave two methyl derivatives (Brady and Reynolds, *J.*, 1928, 198; 1931, 1273). The ratio *O*-Me/*N*-Me formed in 2N-MOH was LiOH 1·12, NaOH 0·97, KOH 1·02, RbOH 1·17, CsOH 1·26, and $\text{NMeEt}_3\cdot\text{OH}$ 1·53. Although the accuracy of the results is not sufficient to dogmatise on the effect of the change from one alkali-metal to another the difference between sodium hydroxide and methyltriethylammonium hydroxide seems well outside the limit of experimental error, and probably the difference between sodium hydroxide and cæsium hydroxide is also significant.



Since sodium hydroxide and methyltriethylammonium hydroxide gave the greatest difference, in subsequent experiments the hydroxides of cæsium and rubidium were not always used on account of the lengthy task of continually recovering the limited amounts of the materials.

Lithium hydroxide could not always be employed owing to the sparing solubility of lithium salts, which crystallised out and altered the conditions of the experiment.

2-Hydroxylepidine can be methylated by methyl iodide in methyl alcohol in the presence of alkali methoxide. With sodium methoxide, the ratio *N*-Me/*O*-Me is 4·5, with potassium methoxide is 10·8, and with $NMeEt_3$·OMe is ∞. In the last case no trace of the *O*-Me compound, but 82% of the *N*-Me compound, was obtained.



The improvement in technique afforded by the determination of aldehydes by dinitro phenylhydrazine has enabled us to show the effect of change of alkali in the Reimer–Tiemann reaction where the original authors failed (*loc. cit.*). In 15N-alkali the *ortho-para*-ratio was NaOH 2·08, KOH 1·24, CsOH 0·98, and $NMeEt_3$·OH 0·52. In 2N-alkali the difference almost disappeared, the ratio being NaOH 0·90, KOH 0·91, and $NMeEt_3$·OH 0·86. In 15N-lithium hydroxide the ratio was 0·9 but, as much lithium phenoxide crystallised out, the concentration in solution was low.

The yields of aldehyde in the Reimer–Tiemann reaction were of the usual low order (Armstrong and Richardson, *J.*, 1933, 496) and the results would not be credible were they not so remarkable and repeatable within reasonable limits. On changing from sodium hydroxide to methyltrimethylammonium hydroxide the product changes from *o-/p-* = 2 : 1 to *o-/p-* 1 : 2.

The experiments so far described did not admit of very accurate measurements, so a kinetic investigation has been made of the hydrolysis of esters by various alkalis in homogeneous media, with the following results:

Hydrolysis of Me_2SO_4 *in* 50% *v/v aqueous* MeOH *at* 0°.

Alkali.	Concn., N.	10^3k_2, sec.$^{-1}$.
NaOH	0·1000	2·61
KOH	0·1022	2·57
$NMeEt_3$·OH	0·1037	2·52

The differences are within the experimental error, so at this concentration of alkali no effect is observed.

Methyl sulphate in aqueous methyl alcohol is decomposed much too rapidly by stronger alkalis for kinetic measurements to be made, so the less reactive ethyl sulphate was substituted, with results as follows:

Hydrolysis of Et_2SO_4 *in* 90% *v/v aqueous* MeOH *at* 0°.

Alkali.	Concn., N.	10^5k_2, sec.$^{-1}$.
NaOH	1·0328	7·5
KOH	1·0328	9·5
$NMeEt_3$·OH	1·0534	16·9

Owing to the difficulty in obtaining accurate results in kinetic measurements at these concentrations, it would be unwise to place too much reliance on the difference between sodium and potassium hydroxides, but the difference between sodium and methyltriethylammonium hydroxides is too large to be due to experimental error.

The use of methyl alcohol as a solvent introduces possible complications, so esters were investigated which could be hydrolysed in homogeneous aqueous solution.

The hydrolysis of methyl methanesulphonate in 1·026N-aqueous sodium hydroxide at 25° gave $k_2^{25} = 5·5 \times 10^{-4}$ sec.$^{-1}$ and in 1·026N-aqueous methyltriethylammonium hydroxide gave $k_2^{25} = 9·4 \times 10^{-4}$ sec.$^{-1}$.

The alkali alkyl phthalates *o*-RO_2C·C_6H_4·CO_2M (R = alkyl, M = Na, K, or $NMeEt_3$) at 25° or 0°, in both water and 90% methyl alcohol, were hydrolysed with the corresponding alkali hydroxide; for comparison ethyl acetate was hydrolysed in 90% methyl alcohol at 0°. The rate constants are given in Table I. In 0·1N-alkali no effect is observable, even in aqueous methyl alcohol. In N-alkali the effects are not marked in aqueous solutions, except in the case

TABLE I.

Water.		90% Methyl alcohol.	
Alkali (+)-sec.-*octyl phthalate at* 25°.			
1·026N-NaOH	$6{\cdot}2 \times 10^{-6}$	—	—
1·026N-$NMeEt_3{\cdot}OH$	$6{\cdot}95 \times 10^{-6}$	—	—
Alkali sec.-*butyl phthalate at* 25°.			
1·026N-NaOH	$1{\cdot}8 \times 10^{-4}$	1·047N-NaOH	$1{\cdot}4 \times 10^{-5}$
		0·985N-KOH	$1{\cdot}1 \times 10^{-5}$
1·026N-$NMeEt_3{\cdot}OH$	$1{\cdot}8 \times 10^{-4}$	1·077N-$NMeEt_3{\cdot}OH$	$0{\cdot}092 \times 10^{-5}$
Alkali methyl phthalate at 25°.			
1·005N-NaOH	$4{\cdot}33 \times 10^{-3}$	0·9847N-NaOH	$1{\cdot}25 \times 10^{-4}$
1·026N-$NMeEt_3{\cdot}OH$	$3{\cdot}5 \times 10^{-3}$	1·108N-$NMeEt_3{\cdot}OH$	$0{\cdot}14 \times 10^{-4}$
Alkali methyl phthalate at 0°.			
1·005N-NaOH	$5{\cdot}0 \times 10^{-4}$	—	—
1·026N-$NMeEt_3{\cdot}OH$	$5{\cdot}0 \times 10^{-4}$	—	—
Ethyl acetate at 0°.			
—	—	1·0328N-NaOH	$1{\cdot}66 \times 10^{-4}$
—	—	1·0328N-KOH	$1{\cdot}66 \times 10^{-4}$
—	—	1·0328N-$NMeEt_3{\cdot}OH$	$1{\cdot}17 \times 10^{-4}$

of methyl methanesulphonate where $k^{25}_{\text{Am}}/k^{25}_{\text{NaOH}} = 1{\cdot}7$ (k_{Am} refers to the quaternary ammonium base), but in 90% methyl alcohol in the hydrolysis of ethyl sulphate $k_{\text{Am}}/k_{\text{NaOH}} = 2{\cdot}2$, of alkali *sec.*-butyl phthalate $k^{25}_{\text{Am}}/k^{25}_{\text{NaOH}} = 0{\cdot}066$ and of alkali methyl phthalate $k^{25}_{\text{Am}}/k^{25}_{\text{NaOH}} = 0{\cdot}112$.

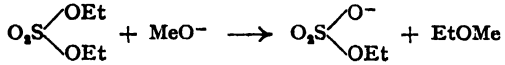
The most significant fact is that in the same solvent methyltriethylammonium hydroxide hydrolyses ethyl sulphate more rapidly, but an alkali alkyl phthalate less rapidly, than does sodium hydroxide. It seems impossible to suppose that the difference in rate constants is due simply to variation of hydroxyl-ion concentrations in the solutions, and one must seek an explanation in the nature of the compound hydrolysed.

The first difference in nature of the substance hydrolysed is that whereas the esters of carboxylic acids on alkaline hydrolysis normally undergo acyl–oxygen fission (see Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 689, for a summary of the evidence) methyl methanesulphonate on aqueous alkaline hydrolysis undergoes alkyl–oxygen fission by a bimolecular mechanism (Ader, University of London Ph.D. Thesis, " Mechanism of Sulphonic Ester Hydrolysis," 1949), and ethyl sulphate on interaction with alcohol in the presence of water and sodium hydroxide undergoes mainly an alkyl–oxygen fission (Lauder and Green, *Nature*, 1946, **157**, 767).

In aqueous methyl alcoholic solutions both hydroxyl and methoxyl ions will exist : $MOH \rightleftharpoons M^+ + HO^-$; $HO^- + HOMe \rightleftharpoons H_2O + MeO^-$. In acyl–oxygen fission attack by MeO^- does not lead to a change in the acid titre :

$$R'{\cdot}CO_2R + MeO^- \rightleftharpoons R'{\cdot}CO_2Me + RO^-$$

but with alkyl–oxygen fission the titre changes :



$$O_2S\begin{matrix}\diagup OEt\\ \diagdown OEt\end{matrix} + MeO^- \longrightarrow O_2S\begin{matrix}\diagup O^-\\ \diagdown OEt\end{matrix} + EtOMe$$

An explanation might be suggested, therefore, that in a solution of methyltriethylammonium hydroxide in 90% methyl alcohol the methoxyl-ion concentration is higher than in a corresponding solution of sodium hydroxide, and vice versa for the hydroxyl-ion concentration. This would account for the slower action of the ammonium base on the carboxylic esters and might account for its more rapid action on ethyl sulphate. If this were the explanation one would expect a similar change of the same order in the rate constant of the hydrolysis of ethyl acetate, but in this case a decrease of only 30% is observed whereas in the phthalates there is a factor of ten.

In experiments using methyl alcohol as a solvent a complication may arise when a different alcohol is produced from the ester, since the rate constant may be a composite figure representing the following reactions :

$$R'{\cdot}CO_2R + HO^- \longrightarrow R'{\cdot}CO_2H + RO^-$$
$$R'{\cdot}CO_2R + MeO^- \rightleftharpoons R'{\cdot}CO_2Me + RO^-$$
$$R'{\cdot}CO_2Me + HO^- \longrightarrow R'{\cdot}CO_2H + MeO^-$$

This might be the case for the hydrolysis of alkali *sec.*-butyl phthalate in methyl alcohol, but not for the hydrolysis of alkali methyl phthalate in methyl alcohol. Since, however, the rate constant for the hydrolysis of sodium *sec.*-butyl phthalate by sodium hydroxide is approximately one-tenth of that of sodium methyl phthalate by sodium hydroxide and the rate constant for the hydrolysis of methyltriethylammonium *sec.*-butyl phthalate by methyltriethylammonium hydroxide is also approximately one-tenth of that of methyltriethylammonium methyl phthalate, it can be assumed that this complication plays but a small part in the difference between the rate constants obtained with sodium hydroxide and methyltriethylammonium hydroxide. It seemed desirable, in the first instance, to confine these experiments to one solvent alcohol, to avoid ambiguities caused by possible variation in the alkoxyl : hydroxyl ratio in changing from one alcohol to another, or by different facilities of various alcohols for forming co-ordination compounds.

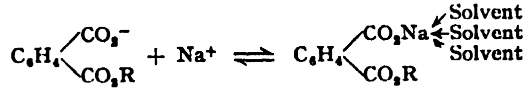
It might be held that different solvation of the cations would have an influence. The primary solvation would be in the order $Na^+ > K^+ \gg MeEt_3N^+$ (cf. Bockris, *Quart. Reviews*, 1949, **3**, 173), and if water molecules solvated the cations more readily than methyl alcohol molecules the concentration of HO^- compared with MeO^- in 90% methyl alcohol would be reduced more by Na^+ than by $MeEt_3N^+$ owing to the removal of water in the equilibrium $HO^- + HOMe \rightleftharpoons MeO^- + H_2O$, but this would decrease the rate of hydrolysis by sodium hydroxide compared with that by methyltriethylammonium hydroxide. If, on the other hand, there was preferential solvation by methyl alcohol, a greater increase in HO^- concentration would result from Na^+ than from $MeEt_3N^+$, but owing to the high proportion of methyl alcohol the difference would probably be very small. Further, solvation would not surmount the difficulty of explaining an opposite effect of the cations in the hydrolysis of ethyl sulphate and methyl methanesulphonate.

Neither of these explanations can be used to account for the differences observed in the alkylation of tautomerides and in the Reimer–Tiemann reaction in which alteration in the orientation of substitution is observed.

An explanation, which covers all cases and can be extended to numerous other reactions where a difference is observed between the alkali hydroxides, concerns the ease with which the different cations can form stable covalent links with the organic compound under investigation.

Other evidence leads to the conclusion that, with the alkali metals, the tendency to form stable covalent bonds decreases from sodium to cæsium; the nitrogen in the tetra-alkylammonium ion, having already a completed octet of electrons, is unlikely to form other stable covalent bonds.

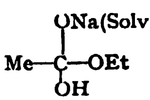
In the case of the half esters of phthalic acid a solution of the tetra-alkylammonium salt may, therefore, be regarded as being almost completely ionised, but a solution of the sodium salt will consist of the equilibrium mixture :



$$C_6H_4\begin{cases}CO_2^-\\CO_2R\end{cases} + Na^+ \rightleftharpoons C_6H_4\begin{cases}CO_2Na \leftarrow (Solvent)_3\\CO_2R\end{cases}$$

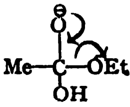
The compound undergoing hydroysis in the two cases will therefore not be the same. In view of the negative charge on the carboxyl group in the ion this will hydrolyse less rapidly than the sodium co-ordination compound. The equilibrium in the sodium salt would move to the right on passing from an aqueous to an alcoholic medium and to the left on reduction of concentration of the reactants in the solvent. The experimental rate constants are in accordance with these considerations.

In ethyl acetate a much smaller effect would be expected although it might still exist, for in the transition state



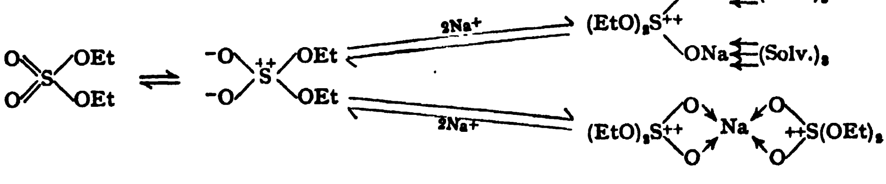
$$Me-\overset{ONa(Solv.)_3}{\underset{OH}{C}}-OEt$$

would be less likely to give the acid than



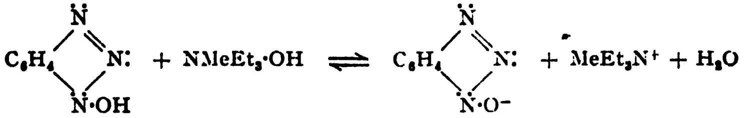
$$Me-\overset{O^{\ominus}}{\underset{OH}{C}}-OEt$$

In ethyl sulphate the sodium ions can accept electrons from the co-ordinately linked oxygens and from the solvent, thus :



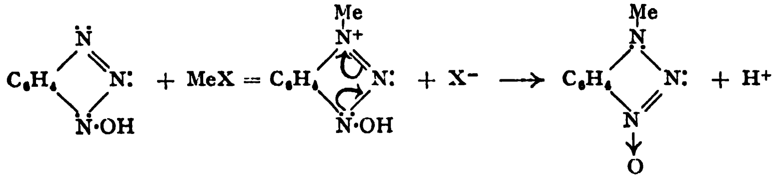
Any such tendency to neutralise the negative charge on oxygen will enhance the positive charge on sulphur which would favour alkyl–oxygen fission, but in view of the tendency of the sulphur atom to increase its octet the hydroxyl ion will be strongly attracted to the S^{++} centre. If only one hydroxyl ion attacks, the sulphur atom will still bear a positive charge and there will be little tendency for acyl–oxygen fission to occur with escape of EtO^-; this might be expected only if two hydroxyl ions attacked at the same time, but such a termolecular reaction would be very slow. The sodium complex is accordingly less easily attacked by sodium hydroxide than by the tetra-alkylammonium hydroxide.

We turn now to the methylation of tautomeric compounds; in solutions of 1-hydroxybenztriazole in tetra-alkylammonium hydroxide the undissociated compound (I) and the ion

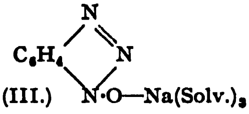


(I.) (II.)

(II) will be present. In (I) attack will occur at the oxygen atom, leading to the formation of 1-methoxylbenztriazole, but in (I) attack at nitrogen will be favoured, followed by elimination of a proton owing to electron withdrawal by the N^+, leading to the formation of 3-methylbenztriazole 1-oxide.



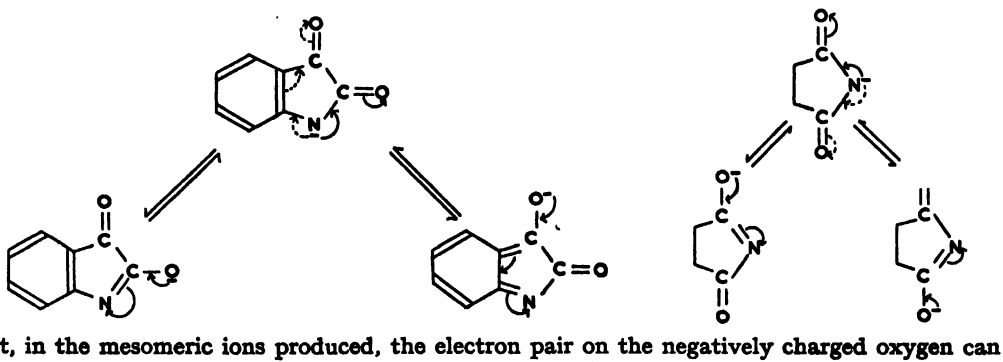
Brady and Reynolds (*loc. cit.*) showed that in the absence of alkali and solvent 1-hydroxybenztriazole suffered only *N*-methylation, and Brady and Day (*J.*, 1923, **123**, 2258) showed that in the substituted hydroxybenztriazoles (*e.g.*, the nitro-compounds) the more acidic the compound, and consequently the less hydrolysed its salts in aqueous solution, the greater the preponderance of *O*-alkylation.



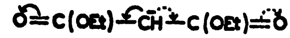
In the presence of sodium hydroxide the solution will contain a third species (III), in which attack at nitrogen will be favoured; so the proportion of *N*-methylation increases. The proportion of (III) falls on passing from sodium to cæsium, so the proportion of *N*-methylation also falls.

A methyltriethylammonium hydroxide solution of 2-hydroxylepidine, which, on our argument, should contain essentially ions only, gave, on methylation, only the *N*-methyl compound.

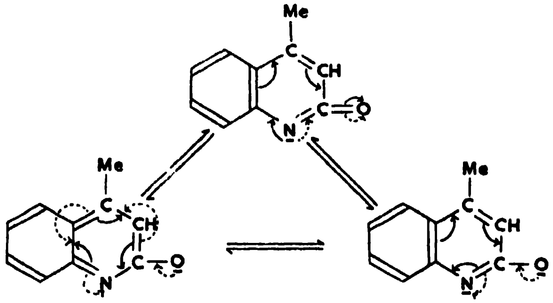
No explanation seems to have been advanced for the *N*- rather than the *O*-alkylation of the sodium salts of lactam–lactim tautomerides such as isatin, phthalimide, and 2-hydroxypyridine. In isatin and the cyclic imides an electron pair on a negatively charged nitrogen can move in two directions, *viz.*:



but, in the mesomeric ions produced, the electron pair on the negatively charged oxygen can move only in one direction. It seems reasonable, therefore, to suppose that the ion with the negative charge associated with nitrogen contributes more than do the ions with the negative charges associated with oxygen to the structure of the resonance ion and, consequently, that the nitrogen atom will be attacked by an electrophilic reagent such as Me^+. A similar explanation can be offered for the exclusive *C*-alkylation of, *e.g.*, ethyl sodiomalonate.

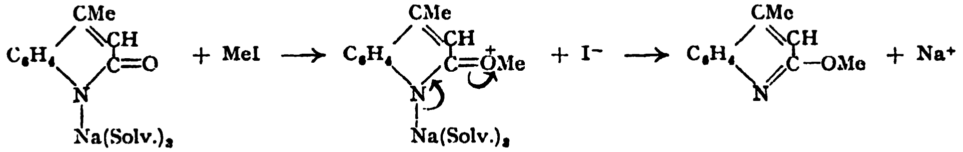


The case of 2-hydroxylepidine or 2-hydroxypyridine is more complex. When the negative charge is on nitrogen the electron pair can again move in two directions, whilst in the ions with the charge associated with oxygen the electron pair can move only in one direction, but the latter ions are interconvertable by electron shift within the benzenoid ring, thus:



It is noteworthy that the ion of hydroxybenztriazole, which becomes alkylated on oxygen, does not exhibit this peculiarity, nor does the oximino-ion $R{\cdot}CH{=}N{-}O^-$, which also becomes alkylated on oxygen (Brady and Goldstein, *J.*, 1926, 2403; Brady and Jackson, unpublished).

As the negative charge on the 2-hydroxylepidine ion is associated mainly with the nitrogen atom, *N*-alkylation is explicable in tetra-alkylammonium hydroxide solution, but in sodium hydroxide solution, owing to the tendency to form a co-ordination compound, some *O*-methylation can occur by the following mechanism:

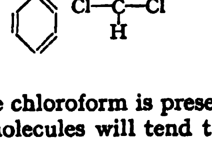


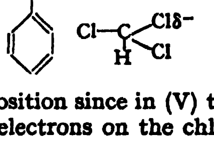
In the Reimer–Tiemann reaction the significant stage is entry of the $-CHCl_2$ into the nucleus

$$C_6H_5{\cdot}OM + CHCl_3 + M^+ + HO^- = MO{\cdot}C_6H_4{\cdot}CHCl_2 + M^+ + Cl^- + H_2O$$

In the presence of 15N-tetra-alkylammonium hydroxide no un-ionised phenol would be present and no co-ordination compound, so that the only reacting species would be the phenoxide ion. In these circumstances substitution yields approximately 2 parts of *p*- to 1 of *o*-compound; the preponderance of *para*-substitution is in accordance with expectation in view of the strong electromeric effect of the negative pole. When 15N-sodium hydroxide is employed a different state of affairs can exist: either chloroform or solvent molecules or both can co-ordinate with the sodium:

(IV.)

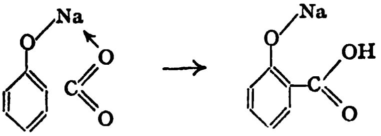




(V.)

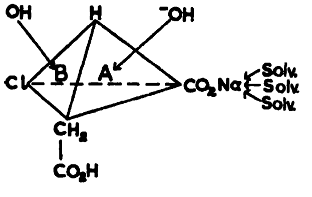
In either case the chloroform is presented to the *ortho*-position since in (V) the positive charges on the solvent molecules will tend to attract the lone electrons on the chlorine. On passing from sodium hydroxide to potassium hydroxide and cæsium hydroxide the extent of co-ordination will decrease and the amount of *ortho*-substitution decreases.

Ingold (*Ann. Reports*, 1926, **23**, 142) has suggested a similar explanation of the nuclear alkylation of phenols through their salts in non-ionising solvents where the substituent enters exclusively at the *ortho*-position. The same idea has been invoked in the Kolbe–Schmidt reaction which has been shown to involve, probably, direct substitution at nuclear carbon and not intermediate formation of sodium phenyl carbonate (Tijmstra Bz, *Ber.*, 1905, **38**, 1375; Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3029).



The above authors state no reasons for the difference in behaviour between sodium and potassium phenoxide, but it could be caused by a reduced stability of the potassium co-ordination compound.

When the Reimer–Tiemann reaction is carried out in less concentrated solutions, *e.g.*, in 2N-alkali, the *ortho*–*para* ratio, when tetra-alkylammonium hydroxide is used, corresponds to the substitution of the phenoxide ion plus that of free phenol formed by hydrolysis. When 2N-sodium hydroxide is used, only a small amount of co-ordination compound is formed, so that the *ortho*–*para* ratio is not appreciably altered.



If the view put forward is correct a number of other phenomena are capable of a similar explanation. In the Walden inversion previously mentioned, if co-ordination compounds are formed at the carboxyl group attached directly to the asymmetric carbon atom, steric hindrance might well hinder the approach of the hydroxyl ion to face *A* as required for inversion, and approach to face *B* involving no inversion would be favoured. The increase in inversion found by Walden (*loc. cit.*) was in the order LiOH < NaOH < KOH < RbOH < NH_4OH, that is, as the probability of co-ordination compound formation decreased.

EXPERIMENTAL.

Preparation of Alkalis.—Solutions of sodium hydroxide and potassium hydroxide were made up with the usual precautions to avoid all but small amounts of carbonate, diluted with water or methyl alcohol, and checked against standardised hydrochloric acid. Rubidium and cæsium hydroxides were prepared from the sulphates and barium hydroxide. Methyltriethylammonium hydroxide solutions were prepared by shaking a weighed amount of the iodide with the solvent and 1·3 equivalents of silver oxide for 10—20 hours until a filtered test portion gave no precipitate with nitric acid and silver nitrate; the precipitate was allowed to settle, and the solution siphoned off, titrated with hydrochloric acid, and the strength adjusted. Precautions were taken to avoid contamination with carbon dioxide.

Methylation of 1-*Hydroxybenztriazole.*—The hydroxybenztriazole was prepared *via* *o*-nitrophenylhydrazine. 1-Methoxybenztriazole and 3-methylbenztriazole 1-oxide were prepared for test of the analytical method (Brady and Reynolds, *J.*, 1928, 196).

The hydroxybenztriazole (1·5 g.; 0·011 mol.) was dissolved in 2N-aqueous alkali (6 c.c.), and redistilled methyl sulphate (1·1 c.c.; 0·011 mol.) added. The mixture was thoroughly shaken for 10 minutes whereupon the solid ethers began to separate, and after 50 minutes were repeatedly extracted with chloroform. The combined extracts were dried (Na_2SO_4), the solvent was removed, and the residue dried in an evacuated desiccator. The relative amounts of *O*- and *N*-methyl derivatives were determined by Zeisel and Herzig–Meyer estimations. As the amounts of silver iodide formed did not correspond to the total quantity of the mixed *N*- and *O*-methyl compound employed, determinations were carried out with the pure derivatives. The *O*-methyl compound gave an almost theoretical yield of silver iodide, but the *N*-methyl compound gave approx. 61%. This determination was reproducible within 1%; the loss is probably caused by migration of some of the methyl into the benzene nucleus on heating of the hydriodide. In column 6 of Table II a correction has been applied to the content of *N*-methyl compound which is calculated from (1 + 39/61) time the actual weight of silver iodide. The total amount of methyl compounds (column 7 of Table II) then varies from 87 to 100%, with an average of 93%.

Methylation of Hydroxylepidine.—2-Hydroxylepidine was prepared by the method of Laver and Kaslow (*Org. Synth.*, **24**, 68); the *O*- and *N*-methyl derivatives were prepared for comparison (Knorr, *Annalen*, 1886, **236**, 97; Knorr and Autrick, *Ber.*, 1884, **17**, 2876). A Zeisel estimation for the pure *O*-methyl compound gave a 98% yield of methyl iodide, and a Herzig–Meyer estimation for the *N*-methyl compound a 95% yield.

The hydroxylepidine (3 g.) was added to 2N-alkali methoxide (9 c.c.) in methyl alcohol (slightly more than 1 equiv.) together with methyl iodide (2·3 c.c.; 1·5 equivs.), and the whole heated under reflux for 30 minutes; a further 3 c.c. of the methoxide solution and 1 c.c. of methyl iodide were then added, and heating was continued for a further 90 minutes. The solution was diluted with water and made strongly alkaline with aqueous sodium hydroxide. The methylation products were extracted with ether, the extract was dried (Na_2SO_4), the solvent removed, and the solid residue dried in a vacuum-desiccator. The yield of crude ethers was about 80% of the theoretical. The quantities of *O*- and *N*-methyl derivatives were determined as before. The results are given in Table III.

TABLE II.

2N-Alkali.	Expt.	Wt. (g.) of crude methyl compounds from 1·5 g. of triazole.	OMe, %.	NMe, %, found.	NMe, %, corr.	Total OMe and NMe, %.	Ratio, OMe/NMe.	Mean.
LiOH	*a*	1·03	50·0	27·6	45·2	95·2	1·10	1·12
			49·8	26·9	44·1	93·9	1·13	
	b	1·01	50·7	27·6	45·2	95·9	1·12	
			50·7	26·9	44·1	94·8	1·14	
NaOH	*a*	1·00	48·2	31·7	51·9	100·1	0·93	0·97
	b	1·06	47·9	29·9	49·0	96·9	0·98	
	c	1·09	48·0	28·7	47·0	95·0	1·02	
	d	1·10	47·6	30·9	50·6	98·2	0·94	
KOH	*a*	1·28	46·3	28·7	47·0	93·3	0·99	1·01
	b	1·40	48·3	30·0	49·2	97·5	0·98	
	c	1·35	49·0	28·8	47·2	96·2	1·04	
			48·4	28·3	46·4	95·8	1·04	
RbOH	—	—	46·9	24·6	40·0	86·9	1·17	1·17
CsOH	*a*	1·30	49·0	24·3	39·8	88·8	1·23	1·26
			49·2	24·1	39·5	88·7	1·24	
	b	1·22	52·6	25·2	41·3	93·9	1·27	
			51·4	23·8	39·0	90·4	1·32	
$NMeEt_3$·OH	*a*	1·35	54·5	21·0	34·4	88·9	1·58	1·53
			55·8	21·6	35·4	91·2	1·64	
	b	1·20	53·7	22·9	37·5	91·2	1·43	
			57·5	24·1	39·5	97·0	1·46	

TABLE III.

Alkali.	Expt.	OMe, %.	NMe, %.	Ratio, NMe/OMe.	Mean.	Alkali.	Expt.	OMe, %.	NMe, %.	Ratio, NMe/OMe.	Mean.
NaOH	*a*	12·7	52·3	4·12	4·5	KOH	*a*	7·6	82·1	10·8	10·8
	b	21·5	75·7	3·52		$NMeEt_3$·OH	*a*	0	82·6	∞	∞
	c	12·6	71·0	5·63							
	d	15·5	66·5	4·78							

In two qualitative experiments using the tetra-alkylammonium hydroxide no *O*-methyl compound was obtained.

Reimer–Tiemann Reaction.—Phenol (3 g.) was dissolved in approx. 15N-alkali (10 c.c.) under a reflux condenser and warmed at 50—60°. Chloroform (3 c.c.) was then added with vigorous shaking which was continued for 15 minutes. The mixture was then heated on a water-bath for 30 minutes. After cooling, the solution, which contained solid, was diluted until the solid dissolved, and then acidified with hydrochloric acid and distilled in steam, about 600 c.c. of distillate being collected. The distillate was transferred to a graduated flask, concentrated hydrochloric acid added (200 c.c.), and the volume made up to 1000 c.c. with water; 50-c.c. lots were removed, and an equal volume of a solution of 2 : 4-dinitrophenylhydrazine hydrochloride was added. This reagent was prepared by suspending 2 : 4-dinitrophenylhydrazine (4 g.) in dilute hydrochloric acid (25 c.c.), adding concentrated hydrochloric acid (20 c.c.) with shaking and then a further 2 l. of 2N-acid. After being kept overnight the solution was filtered from the small amounts of undissolved material. The precipitated dinitrophenylhydrazone was kept for an hour to coagulate, filtered through a sintered-glass crucible, washed 3 times with 2N-hydrochloric acid, dried for 2 hours at 110°, and weighed. The residue from the steam-distillation was filtered whilst hot, cooled, and made up to 1 l. by concentrated hydrochloric acid (200 c.c.) and water. The *p*-hydroxybenzaldehyde was determined as above in 50-c.c. portions. Similar experiments were performed using 2N-alkali. The results are shown in Table IV.

Kinetic Experiments.—Methyl sulphate was repeatedly shaken with water until the aqueous layer was free from sulphate, dried (Na_2SO_4), and twice distilled at 6—7 mm., the portion boiling at 45—47° being collected. Ethyl sulphate was similarly purified, the fraction boiling at 57·5—60° being collected. *sec.*-Butyl hydrogen phthalate and methyl hydrogen phthalate were prepared by the standard method. We are indebted to Dr. J. Kenyon for a specimen of (+)-*sec.*-octyl hydrogen phthalate and to Dr. G. Ader for one of methyl methanesulphonate.

As an example of the technique employed the hydrolysis of methyl sulphate with an equivalent quantity of 0·1N-sodium hydroxide in 50% (v/v) aqueous methyl alcohol at 0° is described.

The methyl sulphate (*ca.* 0·5 c.c.; 1 mol.) was run into a thin, weighed, glass bulb, which was sealed and re-weighed. An amount of the 0·1N-sodium hydroxide solution exactly equivalent (1 mol.) to the methyl sulphate was cooled to 0° and the bulb crushed beneath its surface. After mixing, the solution was transferred to a stoppered flask, cooled in ice–water well stirred with a mechanical stirrer in a large lagged beaker. For experiments at 25° a thermostat was used. From time to time portions (5 c.c.)

of the solution were removed, the reaction was stopped by running the mixture into an equivalent of 0·1N-hydrochloric acid, and the acid formed during hydrolysis titrated against 0·05N-barium hydroxide (bromocresol-purple as indicator). The rate constants were calculated from the usual second-order equation, with results given in Table V.

TABLE IV.

Alkali :	15N. *ortho-*, %.	15N. *para-*, %.	15N. *ortho-* : *para-*.	15N. Mean.	2N. *ortho-*, %.	2N. *para-*, %.	2N. *ortho-* : *para-*.	2N. Mean.
NaOH	12·95	6·38	2·03	2·08	5·06	5·69	0·89	0·90
	9·38	4·03	2·33		4·52	5·02	0·90	
	10·95	4·94	2·21		4·11	4·52	0·91	
	10·25	5·56	1·85					
	8·84	4·44	1·99					
KOH	11·41	9·46	1·21	1·24	4·15	4·73	0·877	0·91
	12·24	9·71	1·26		4·86	5·25	0·923	
	10·79	8·55	1·26		4·90	5·25	0·931	
CsOH	7·35	7·64	0·96	0·98				
	8·19	8·05	1·01					
$NMeEt_3\cdot OH$	3·90	6·43	0·61	0·52	2·16	2·43	0·87	0·86
	3·86	6·76	0·57		1·39	1·63	0·85	
	2·62	6·60	0·40					

TABLE V.

Time, secs., $\times 10^{-2}$.	Titration figures, c.c. (four expts.).				$10^3k_2^0$, sec.$^{-1}$ (four expts.).			
6	1·4	1·4	1·4	1·4	2·70	2·70	2·70	2·70
12	2·35	2·45	2·35	2·35	2·51	2·70	2·51	2·51
18	3·0	3·2	3·1	3·1	2·36	2·61	2·48	2·48
24	3·8	—	4·05	3·8	2·51	—	2·81	2·51
30	4·45	4·5	4·5	4·45	2·63	2·71	2·71	2·68
36	4·9	4·85	4·8	4·9	2·63	2·60	2·55	2·63
42	5·15	5·1	5·2	5·0	2·50	2·48	2·56	2·56
54	5·8	5·7	5·7	5·9	2·53	2·43	2·43	2·65
66	6·4	6·4	6·5	6·25	2·65	2·66	2·77	2·50
78	6·65	6·7	6·95	6·8	2·51	2·58	2·87	2·71
144	8·0	8·0	8·1	8·2	2·75	2·75	2·90	3·11
258	—	8·7	—	—	—	2·60	—	—
864	10·1	10·05	10·2	10·0				
				Mean :	2·57	2·62	2·66	2·61

Overall mean $k_2^0 = 2·61 \times 10^{-3}$ sec.$^{-1}$.

With 0·1022N-KOH, the overall mean $k_2 = 2·57 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +0·23 and −0·14.

With 0·1037N-$NMeEt_3\cdot OH$ the overall mean $k_2 = 2·52 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +0·10 and −0·17.

TABLE VI.

Time, secs., $\times 10^{-2}$.	Titration figures, c.c. (2 expts.).		$10^5k_2^0$, sec.$^{-1}$ (2 expts.).	
9	0·85	0·9	7·36	8·13
18	1·55	1·65	8·60	8·7
27	1·95	2·2	7·33	8·6
36	2·4	2·7	7·25	8·5
45	2·8	2·9	7·15	7·5
54	3·5	3·35	8·28	7·7
90	4·25	4·55	6·63	7·4
124·5	5·3	5·4	6·98	7·15
166·2	6·2	5·95	7·13	6·71
364	10·2	10·4		
		Mean :	7·41	7·70

The hydrolysis of ethyl sulphate was investigated at 0° with 1·5 equivalents of alkali in 90% (v/v) aqueous methanol. With 1·0328N-sodium hydroxide the results given in Table VI were obtained.

The deviation from the mean k_2^0 is as much as 16% but, as the concentrations were high and appreciable errors were likely owing to volume changes in mixing and to separation of solid sodium ethyl sulphate during the reaction, it was considered that the results were as satisfactory as could be expected.

With 1·0328N-potassium hydroxide the mean $k_2^0 = 9·5 \times 10^{-5}$ sec.$^{-1}$ with maximum deviations of +0·6 and −0·5, and with 1·0534N-$NMeEt_3\cdot OH$ $k_2^0 = 16·9 \times 10^{-5}$ sec.$^{-1}$ with maximum deviations of +1·2 and −1·8.

The maximum value for sodium hydroxide was k_2^0 8·7, and the minimum for potassium hydroxide was 9·0; it is thus uncertain whether there is any appreciable difference between these two alkalis, but the minimum for methyltriethylammonium hydroxide was k_2^0 15·1, which is about 1·75 times the maximum for sodium hydroxide and beyond the limit of experimental error.

Methyl methanesulphonate was added to an equivalent quantity of 1·026N-alkali and the reaction carried out in a thermostat at 25°. Portions (2 c.c.) were removed at intervals, run into ice-cold water (20 c.c.), and titrated against 0·0989N-hydrochloric acid (bromocresol-purple). Results are in Table VII.

TABLE VII.

1·026N-NaOH.			1·026N-$NMeEt_3$·OH.		
Time, secs., $\times 10^{-2}$.	Titre.	$10^4k_2^{25}$, sec.$^{-1}$.	Time, secs., $\times 10^{-2}$.	Titre.	$10^4k_2^{25}$, sec.$^{-1}$.
3·6	16·3	5·08	3·8	14·7	(8·35)
7·3	14·0	5·30	7·35	11·6	9·30
11	12·3	5·34	11	9·7	9·35
14·6	10·8	5·58	14·65	8·3	9·40
18·45	9·8	5·45	18·55	7·2	9·44
24	8·4	5·62	24	6·1	9·38
33	6·95	5·61	32·95	4·8	9·57
51	5·15	5·63	51·1	3·4	9·58
87	3·35	5·73	87	2·2	9·34
159	2·0	5·69	684	0·2	0·2
3 days	0·0				
	Mean :	5·5		Mean :	9·4

A weighed quantity of alkyl hydrogen phthalate was dissolved in exactly 2 equivalents of aqueous alkali, one being required to form the salt with the free carboxyl group, and the reaction carried out in a thermostat at 25°. Portions (2 c.c.) were removed at intervals, diluted with water (20 c.c.), and titrated against 0·1N-hydrochloric acid (phenolphthalein). (+)-*sec.*-Octyl hydrogen phthalate with 1·026N-sodium hydroxide gave a mean k_2^{25} 6·2 × 10^{-6} sec.$^{-1}$ with maximum deviations of +0·3 and −0·4. With 1·026N-$NMeEt_3$·OH k_2^{25} = 6·95 × 10^{-6} sec.$^{-1}$ with maximum deviations of +0·4 and −0·2. The rate constants, in view of the degree of accuracy, are too similar for a decision whether the difference is significant, especially as a complication arose owing to separation of octyl alcohol during the reaction.

sec.-Butyl hydrogen phthalate and methyl hydrogen phthalate were hydrolysed under similar conditions. Results are given in the Introduction.

The hydrolyses in 90% (v/v) methyl alcohol were carried out as in aqueous solution, a weighed quantity of the ester being dissolved in two equivalents of alkali in aqueous methyl alcohol and kept at 25°. With sodium hydroxide, solid sodium phthalate began to separate after about 8 hours and the values of the rate constants were not very concordant; this did not occur with potassium hydroxide or with methyltriethylammonium hydroxide. The results for *sec.*-butyl hydrogen phthalate are given in Table VIII.

TABLE VIII.

1·047N-NaOH.		0·985N-KOH.		1·077N-$NMeEt_3$·OH.	
Time, hours.	$10^5k_2^{25}$, sec.$^{-1}$.	Time, hours.	$10^5k_2^{25}$, sec.$^{-1}$.	Time, hours.	$10^5k_2^{25}$, sec.$^{-1}$.
2	1·25	2	1·00	2 3	practically no reaction
3	1·16	3	0·91		
12·25	1·66	7	1·09	12·25	(0·041)
26·33	1·77	20·33	1·16	26·33	0·091
31·5	1·93	26·33	1·19	31·5	0·094
61·2	1·39	31·5	1·14	61·2	0·097
81·5	1·30	55·66	1·14	81·5	0·089
108	1·16	92	1·05	108	0·091
146	1·09			146	0·097
193·5	1·03			193·5	0·097
Mean :	1·38	Mean :	1·08	Mean :	0·093

With methyl hydrogen phthalate and sodium hydroxide, over the range 15—315 minutes, whereafter large amounts of sodium phthalate had separated, the mean k_2^{25} was 1·25 × 10^{-4} sec.$^{-1}$ with maximum deviations of ±0·3, and with methyl hydrogen phthalate and methyltriethylammonium hydroxide over the range 35—4440 minutes, the mean k_2^{25} was 0·14 × 10^{-4} sec.$^{-1}$ with a maximum deviation of ±0·01.

Methyl acetate in 90% (v/v) methyl alcohol was hydrolysed at 0° with 1·033N-alkali. Over the range 15—240 minutes with sodium hydroxide k_2^0 was 1·6 × 10^{-4} sec.$^{-1}$ with a deviation of ±0·2, with potassium hydroxide 1·7 × 10^{-4} sec.$^{-1}$ with a deviation of +0·3 and −0·2, and with methyltriethylammonium hydroxide 1·1 × 10^{-4} sec.$^{-1}$ with a deviation of +0·1 and −0·2.

THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.

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153. The Mechanism of Decarboxylation. Part V. Kinetics of the Decarboxylation of Hydroxybenzoic Acids.

By B. R. Brown, D. Ll. Hammick, and A. J. B. Scholefield.

The rates of decarboxylation of salicylic, 2 : 4-dihydroxybenzoic, and 2 : 4 : 6-trihydroxybenzoic acids have been measured in resorcinol solution over a temperature range of 110—240°. The fall in activation energies (increase in rate) with increase in *o*- and *p*-substitution by hydroxyl groups supports the conclusion that with these acids the decarboxylation is an S_E2 mechanism. The Hinshelwood–Fairclough relation between $\log_{10} PZ$ and $1/E^{\frac{1}{2}}$ is obeyed.

Recently Schenkel and Schenkel-Rudin (*Helv. Chim. Acta*, 1948, **31**, 514) suggested that decarboxylation may occur by two mechanisms, analogous to the S_N1 and S_N2 replacement reactions of Hughes and Ingold (*J.*, 1935, 244) :

$$S_E1 \qquad R{\cdot}CO_2^- = R^- + CO_2$$
$$S_E2 \qquad H^+ + R{\cdot}CO_2^- = HR + CO_2$$

Substantial evidence for the S_E1 mechanism is available (*e.g.*, Pedersen, *J. Physical Chem.*, 1934, **38**, 559; Verhoek, *J. Amer. Chem. Soc.*, 1939, **61**, 186; Parts I, II, III, and IV of this series, Hammick *et al.*, *J.*, 1937, 1724; 1939, 809; 1949, 173 and 659). Examples of the S_E2 mechanism are rapidly accumulating (Schubert, *J. Amer. Chem. Soc.*, 1949, **71**, 2639; Johnson and Heinz, *ibid.*, p. 2913).

The S_E2 mechanism will be facilitated by a high electron density on the carbon atom next to the carboxyl group. Moroever, since the mechanism is essentially bimolecular and involves an acid molecule and a solvated proton, acids which are decarboxylated in this manner will be stable in alkaline but unstable in acid solution. Support for this view is found in the semi-quantitative results of Cazeneuve (*Bull. Soc. chim.*, 1896, **15**, 73) and of Hemelmeyr (*Sitz. Akad. Wiss. Wien*, 1912, **121**, 1359), who show that *o*- and *p*-hydroxybenzoic acids behave thus. The *m*-hydroxybenzoic acids, however, in which the hydroxyl groups cannot make any appreciable contribution to the electron density on the carbon atom next to the carboxyl group, are stable even in acid solution. The suggestion that the decarboxylation of *o*- and *p*-hydroxybenzoic acids may occur by a bimolecular mechanism involving attack of a proton on the negative α-carbon atom has also been made by Fieser and Fieser (" Organic Chemistry," D. C. Heath and Co., Boston, 1944, p. 674).

The aim of the kinetic work here presented was to study the effect of the successive substitution of hydroxyl groups into the *o*- and *p*-positions of benzoic acid on the rate of decarboxylation in resorcinol, which was selected as solvent for reasons given in the Discussion below. The work of Hinshelwood, Laidler, and Timm (*J.*, 1938, 848) indicates that a comparison of activation energies with type and amount of substitution should provide evidence for or against an S_E2 mechanism.

Experimental.

Materials.—Salicylic acid was crystallised twice from water and had m. p. 156°. 2 : 4-Dihydroxybenzoic acid (β-resorcylic acid) was crystallised three times from water and had m. p. 216°. 2 : 4 : 6-Trihydroxybenzoic acid was crystallised once from alcohol and twice from ether and had m. p. 189°. The solvent, resorcinol, was distilled at atmospheric pressure, and had b. p. 276°, m. p. 110°.

Apparatus.—The method used to follow the reaction was by measurement of evolved carbon dioxide, at room temperature and pressure. The apparatus of Walton (*Z. physikal. Chem.*, 1904, **47**, 185) was modified for use at high temperatures (110—240°) and was very similar to the apparatus used by Schubert (*loc. cit.*). Temperature control was obtained by immersing the reaction vessel (containing about 0·3 g. of acid in 10 g. of resorcinol) in a lagged vapour-bath containing a suitable liquid boiling under reflux at the prevailing atmospheric pressure. Temperatures constant to ±0·1° could be maintained for at least 4 hours. The bath liquids were distilled at atmospheric pressure, and fractions boiling over 0·2° were used to construct the Arrhenius plots. The hot solvent (resorcinol) was saturated with carbon dioxide before measurements were made.

The main source of error was likely to arise from variation of the temperature gradient between the evolved carbon dioxide (at the temperature of the reaction) and the measuring burette (at room temperature). This was minimised by using a standard procedure, and by protecting the connecting tubes from temperature changes.

Results.—Since the system had to be stabilised before readings were taken, it was impracticable to obtain an accurate value for the initial concentration of the acid. Moreover, it was inconvenient to prolong the decarboxylation in order to read the total volume of carbon dioxide evolved at the completion of the reaction. These difficulties were overcome by using the method of plotting devised by Guggenheim (*Phil. Mag.*, 1926, **2**, 538). Two series of values for the volume of carbon dioxide evolved, v and v', separated by a time interval t, are obtained. A plot of $\log_{10} (v' - v)$ against time yields a line of gradient $-0{\cdot}434k$, where k is the velocity constant for the decarboxylation at the temperature used. A typical series of results is shown in Table I. The observed values of $\log_{10}(v' - v)$ are compared with those calculated from the equation to the line of gradient $-0{\cdot}434k$.

TABLE I.

Decarboxylation of 2 : 4-dihydroxybenzoic acid in resorcinol (at 465·2° K.)

Time (sec.).	v (ml.).	v' (ml.).	$(v' - v)$ (ml.).	$\log_{10}(v' - v)$ (obs.).	$\log_{10}(v' - v)$ (calc.).
300	5·9	26·4	20·5	1·311	1·325
450	10·0	27·5	17·5	1·243	1·242
600	14·0	28·3	14·3	1·155	1·158
750	17·2	29·0	11·8	1·072	1·074
900	19·8	29·6	9·8	0·901	0·991
1050	21·9	30·1	8·2	0·914	0·908
1200	23·7	30·5	6·8	0·833	0·824

$t = 1200$ sec. $k = 12{\cdot}8 \times 10^{-4}$ sec.$^{-1}$.

Four determinations of k at this temperature yielded the values $k = 11{\cdot}0$, $12{\cdot}8$, $14{\cdot}0$, and $14{\cdot}6 \times 10^{-4}$ sec.$^{-1}$. Average $k = 13{\cdot}1 \times 10^{-4}$ sec.$^{-1}$.

A plot of $1/T$ and $\log_{10} k$ (from Table II) gives the results collected in Table III.

TABLE II.

Effect of temperature.

o-Hydroxybenzoic acid.		2 : 4-Dihydroxybenzoic acid.		2 : 4 : 6-Trihydroxybenzoic acid.	
°K.	10^4k.	°K.	10^4k.	°K.	10^4k.
479·7	1·32	453·6	5·65	382·7	15·4
489·5	2·53	454·2	6·61	383·2	17·9
491·5	3·15	455·4	7·41	384·1	18·3
492·7	3·25	465·2	13·1	391·0	24·2
493·0	3·53	468·4	16·2	396·7	29·5
496·2	3·96	471·1	20·4	397·7	36·7
497·2	5·02	478·2	31·1		
508·2	8·95	480·3	36·7		
509·2	10·5				

TABLE III.

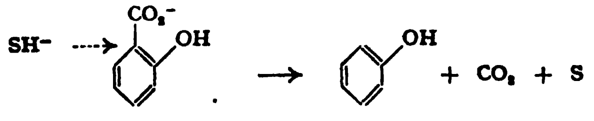
Acid.	E (cals.).	$10^3/E^{\frac{1}{2}}$.	$\log_{10} PZ$ (from k in sec.$^{-1}$).
Benzoic	>39,000 *	—	—
o-Hydroxybenzoic	33,600	5·46	11·5
2 : 4-Dihydroxybenzoic	29,200	5·85	10·9
2 : 4 : 6-Trihydroxybenzoic	13,600	8·58	5·0

* Estimated from the observation that benzoic acid is undecomposed at 250° in resorcinol.

DISCUSSION.

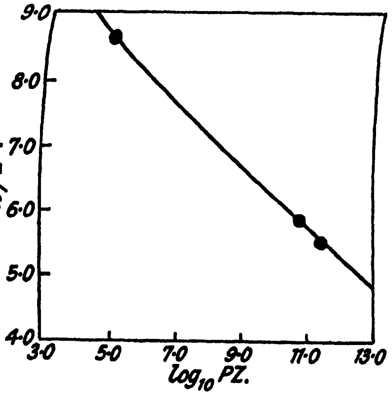
The solvent resorcinol was chosen for these measurements for the following reasons : (1) the solvent had to be acidic in order that the bimiolecular S_E2 reaction would show pseudo-first-order kinetics, owing to the presence of a constant excess of acidic molecules, (2) the solvent had to be the same for each acid in order to give comparable results, hence a solvent liquid over a wide temperature range was required, and (3) it was desirable that the solvent should resemble the reaction products as closely as possible in order that they should cause the least possible change in medium.

The results in Table III indicate that the successive substitution of hydroxyl groups into the *o*- and *p*-positions of benzoic acid causes a progressive decrease in the energy of activation for decarboxylation. Since this substitution increases the electron density on the carbon atom next to the carboxyl group, it can be inferred that the substitution is reducing the repulsion between an attacking solvated proton and the acid molecule (cf. Hinshelwood, Laidler, and Timm, *loc. cit.*). The occurrence of this effect is consistent with the S_E2 mechanism :



The remarkable drop in the *PZ* factor (of the equation $k = PZ \, . \, e^{-E/RT}$) on passing from 2 : 4-dihydroxy- to 2 : 4 : 6-trihydroxy-benzoic acid is perhaps to be associated with a steric effect of the second *o*-hydroxyl group in inhibiting the approach of the solvated proton.

The view that decarboxylation can take place by an S_E2 mechanism involving the attack of a solvated proton on the α-carbon atom is supported by kinetic studies on anthracene-9-carboxylic acid (Schenkel and Schenkel-Rudin, *loc. cit.*), certain cinnamic acids (Johnson and Heinz, *loc. cit.*), mesitoic acid (Schubert, *loc. cit.*), and on the *o*- and *p*-hydroxybenzoic acids. However, these authors put forward no evidence, nor have we been able to obtain any, as to the precise nature of the carboxylic entity which suffers reaction, *i.e.* to distinguish between (1) and (2) :



(1) $SH^+ + R{\cdot}CO_2^- = RH + S + CO_2$

(2) $SH^+ + R{\cdot}CO_2H = RH + S + CO_2 + H^+$

On the other hand, studies of S_E1 decarboxylations have always indicated that the carboxyl group is in the anionic form before decarboxylation :

$$R{\cdot}CO_2^- = R^- + CO_2$$

In order to clarify the details of the S_E2 mechanism further experiments are clearly required.

Hinshelwood and Fairclough (*J.*, 1937, 538, 1573) advance theoretical reasons for the expectation of a linear relationship between $1/E^{\frac{1}{2}}$ and $\log_{10} PZ$ in a series of closely related reactions. The accompanying figure indicates that such a relationship holds for the decarboxylation of hydroxybenzoic acids. This result is interesting on account of the large range of *E* and *PZ* values covered by our data, and on account of the value $-0{\cdot}21 \times 10^4$ found for the slope of the line, $d(\log_{10} PZ)/d(1/E^{\frac{1}{2}})$, which is very close to that found by Hinshelwood and Fairclough (*locc. cit.*) for several reactions.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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154. *Mechanism of the Molecular Rearrangement produced by the Action of Alkali on Chloral-quinaldine* [2-(3 : 3 : 3-*Trichloro-2-hydroxypropyl*)-*quinoline*].

By B. R. BROWN, D. LL. HAMMICK, and SIR ROBERT ROBINSON.

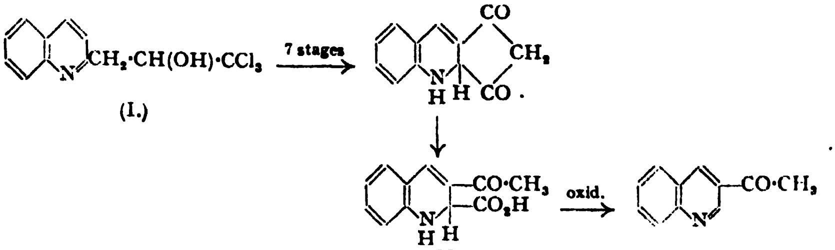
It is shown that the re-arrangement named in the title is equivalent to an αγ-change of a substituted 1-*o*-aminobenzylidenepropanone to a substituted 3-*o*-aminobenzylidenepropanone. This statement is only intended as a description of the basic change in the carbon skeleton and it does not represent the authors' view of the actual mechanism of the process.

2 : 3-Dimethylquinoline was condensed with chloral and the adduct treated with aqueous-alcoholic sodium hydroxide.

The main product was the normal methylquinolylacrylic acid but oxidation of the coloured material in the mother-liquor afforded 3-quinolyl ethyl ketone in small yield.

AN orange salt, $C_{12}H_{10}O_2NNa,3H_2O$, was obtained by Einhorn (*Ber.*, 1886, 19, 904; Einhorn and Sherman, *Annalen*, 1895, 287, 38) as a by-product of the hydrolysis of chloral-quinaldine [2-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline] (I) by means of aqueous alcoholic sodium hydroxide. It was oxidised *via* a carbonyl compound to an acid which was much later proved by Borsche and Manteuffel (*Annalen*, 1936, 526, 22) to be quinoline-3-carboxylic acid.

A molecular rearrangement at some stage was thus revealed but the German workers did not follow up the implications. Woodward and Kornfeld (*J. Amer. Chem. Soc.*, 1948, 70, 2508) showed that the carbonyl compound obtained by oxidation of the orange sodium salt is 3-quinolyl methyl ketone (III) and made it very probable that the Einhorn salt is a dihydroquinoline derivative (cf. II). Their view (*A*) of the mechanism of the process is schematically illustrated below.



(I.) (II.) (III.)

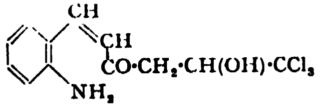
An alternative hypothesis (*B*) was considered by Woodward and Kornfeld but was rejected for good reasons. This involved the disruption of (I) into *o*-aminobenzylideneacetone and chloral, or their equivalents, and recombination of these elements of the structure in a new position.

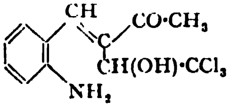
In the particular case of chloral-quinaldine this allows of an intermediate stage identical with a possibility in our own hypothesis (*C*, below), but this is derived in a different manner and would not give the same results, for example in an investigation with labelled atoms.

Our interest in this subject arose from the fact that we found Woodward and Kornfeld's theoretical explanations unconvincing, especially that advanced to justify the assumption of the formation of the *cyclo*pentane ring of a postulated intermediate by attack on the β-position of the quinoline nucleus. This seemed to overlook the much greater probability of the formation of a pyrrolidine ring, if cyclisation were to occur at all.

The view (*C*) of the rearrangement which appeared most acceptable to us can best be explained didactically by noting that chloral-quinaldine by imaginary hydrolytic fissions would yield the unsaturated ketone (IV) which is the 1-*o*-aminobenzylidene derivative of $CH_3·CO·CH_2·CH(OH)·CCl_3$. We suggest that the *o*-aminobenzylidene group is transferred from the 1- to the 3-position in the pentanone chain. This gives (V) which is dehydrated and hydrolysed to give (II).

(IV.)

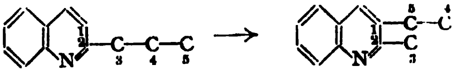




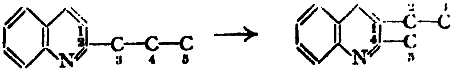
(V.)

It would be of interest to study the rearrangement by means of labelled carbon atoms and the following scheme shows what results are to be expected on the basis of the three hypotheses (*A*), (*B*), and (*C*).

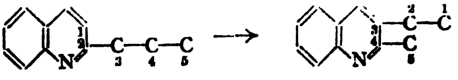
(*A*) Woodward and Kornfeld (favoured):



(*B*) Woodward and Kornfeld (rejected):



(*C*) Present authors:

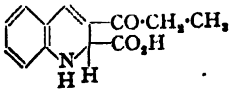


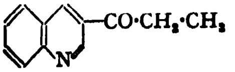
It will be noticed that (*A*) could readily be distinguished from (*B*) and (*C*) by the isotope method but that a distinction between (*B*) and (*C*) would require a quinaldine labelled at the methyl group or at the carbon atom in the 3-position of the quinoline nucleus, but not at both points simultaneously in the same way. The slight preparative difficulty so indicated can best be overcome by a quinaldine synthesis from quinoline.

In the meantime the hypothesis (*C*) is seen to be in harmony with the results obtained by Woodward and Kornfeld with related substances in the quinoline and pyridine series.

According to hypotheses (*A*) and (*B*), 2 : 3-dimethylquinoline-chloral could not undergo the rearrangement but if (*C*) is correct we could obtain (VI) and by oxidation 3-quinolyl ethyl ketone (VII). Actually the colour change indicates that the reaction proceeds as expected, but

(VI.)

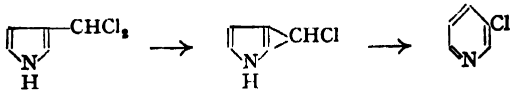




(VII.)

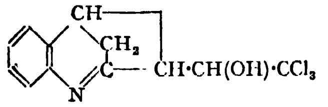
the yield is certainly low and we were unable to isolate the salt of (VI). On oxidation, a small amount of (VII) was isolated and identified as the 2 : 4-*dinitrophenylhydrazone*. The ketone (VII) was synthesised by an unambiguous method described in the Experimental section. We are fully convinced that this result establishes the correctness of hypothesis (*C*) but in view of the small yield we hope to obtain confirmation by the isotope method applied to the original case.

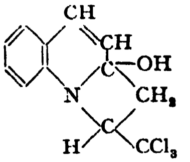
On the assumption that (*C*) is essentially correct, the stages of the process call for consideration. We do not favour a theory of fission and recombination of the parts; it seems almost certain that the molecule undergoes a change somewhat similar to that which may be postulated for the ring-enlargement of pyrrole to 3-chloropyridine :



In the quinaldine-chloral case, two four-ring intermediates are plausible (VIII and IX) :

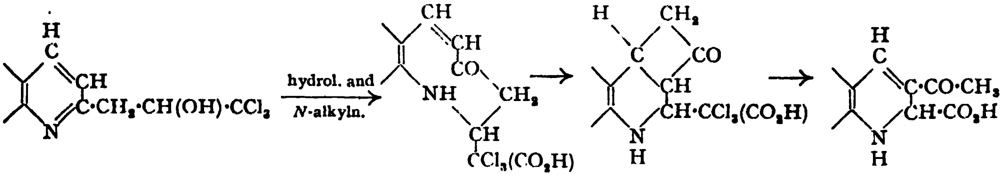
(VIII.)





(IX.)

These represent two parts of the completed rearrangement, and the third is hydrolysis of the imine linkage. These three elements occur in undetermined succession but, since the benzylidene group should be more active after hydrolysis of the imine, a probable sequence is that shown below.



The formation of a four-ring and other precisions of this scheme are not necessary to our theory which can be interpreted with the aid of several different detailed mechanisms.

EXPERIMENTAL.

Ethyl 3-Propionylquinaldate.—A mixture of *o*-aminobenzaldehyde (3·9 g.), ethyl propionylpyruvate (5·6 g.) (Diels, Sielisch, and Müller, *Ber.*, 1906, **39**, 1333), alcohol (50 ml.), and potassium hydroxide (0·05 g.) was boiled under reflux for 10 hours. Colourless, slender needles (3·2 g.) separated from the cooled reaction mixture. A further 1·2 g. were obtained by dilution of the mother-liquor with water. *Ethyl 3-propionylquinaldinate* separated from alcohol as colourless needles, m. p. 107—108° (Found : C, 70·2; H, 5·8. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%).

3-*Propionylquinaldic Acid*.—The above ester (1·1 g.) was heated on the steam-bath with water (50 ml.) and potassium hydroxide (2·0 g.). After ½ hour the hot solution was filtered and acidified with dilute sulphuric acid. Slender, colourless needles (0·9 g.) separated on cooling. Recrystallisation from water yielded 3-*propionylquinaldic acid* as colourless needles, m. p. 153° (decomp.) (Found: C, 67·9; H, 4·8. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%). The acid forms a very sparingly soluble, pale green copper salt.

3-*Quinolyl Ethyl Ketone* (VII).—3-Propionylquinaldic acid (2·3 g.) was refluxed with moist anisole (20 ml.) until decarboxylation was complete (3 hours). The mixture was extracted with 10% hydrochloric acid and benzene, and the acid layer was basified, giving a colourless oil which quickly solidified. The dry solid (1·8 g.) was crystallised from light petroleum (b. p. 60—80°) and then from aqueous methanol, from which it separated as silky, colourless needles, m. p. 79—80° (Found : C, 77·6; H, 5·9. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine–alcohol as deep orange-red needles, m. p. 248—249° (Found : C, 59·6; H, 4·0; N, 19·5. $C_{18}H_{15}O_4N_5$ requires C, 59·2; H, 4·1; N, 19·2%).

3-Methyl-2-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline.—A mixture of 2 : 3-dimethylquinoline (6·0 g.), chloral (6·0 g.), and pyridine (6·0 ml.) was heated on the steam-bath for 2 hours. The solid obtained by addition to water was washed free from pyridine and recrystallised several times from 75% aqueous alcohol, to yield the *adduct* (9·0 g.) as colourless needles which, dried at 80° in a vacuum, had m. p. 134—135° (Found: N, 4·7. $C_{13}H_{12}ONCl_3$ requires N, 4·6%).

Action of Alkali on 3-Methyl-2-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline.—A suspension of the quinoline derivative (15·5 g.) in a hot mixture of alcohol (60 ml.) and water (50 ml.) was treated rapidly with aqueous sodium hydroxide (10 g. in 35 ml. of water). The resulting clear orange-yellow solution was evaporated to dryness, and the solid sodium salts were dissolved in a little water and treated with a slight excess of acetic acid to liberate a mixture of crude brown acids. Treatment of this mixture with concentrated hydrochloric acid (15 ml.) and filtration gave a pale brown residue (11·5 g.) and a deep brownish-red filtrate. Crystallisation of the solid from alcohol yielded the *β-(3-methyl-2-quinolyl)-acrylic acid hydrochloride* as slightly yellow, opaque laminæ, m. p. 220° (decomp.) (Found: N, 5·1. $C_{13}H_{11}O_2N,HCl,C_2H_6O$ requires N, 5·0%). Partial neutralisation with aqueous sodium carbonate and crystallisation from aqueous alcohol yielded *β-(3-methyl-2-quinolyl)acrylic acid* as colourless needles, m. p. 173—178° (decomp.) (Found: C, 72·8; H, 5·2. $C_{13}H_{11}O_2N$ requires C, 73·3; H, 5·2%).

The deep brownish-red filtrate was nearly neutralised with sodium carbonate, and the dark brown solid separated, washed with water, and dried (0·4 g.). This mixture of acids was dissolved in dilute acetic acid, and air was bubbled through the solution for 11 days, during which the colour faded appreciably. The solution was made alkaline with aqueous sodium hydroxide, and the basic products wc. en up in ether. Evaporation of the ether left a small amount of oil, which was dissolved in alcol ınd treated with alcoholic 2 : 4-dinitrophenylhydrazine sulphate. The orange-red solid (0·1 g.) whicl. ·parated was twice crystallised from alcohol–pyridine, from which it separated as deep orange-red micro-needles, m. p. 247—248° (Found: C, 59·8; H, 4·1; N, 18·5. Calc. for $C_{18}H_{15}O_4N_5$: C, 59·2; H, 4·1; N, 19·2%). The m. p. was not depressed on admixture with a specimen of the 2 : 4-dinitrophenyl hydrazone of 3-quinolyl ethyl ketone, prepared as described above. A comparison of the behaviour of the two specimens with solvents and in habit of crystallisation confirmed their identity.

The 2 : *4-dinitrophenylhydrazone* of 3-quinolyl methyl ketone separated from nitrobenzene as minute red prisms, m.p. 261—262° (Found: C, 58·1; H, 3·7. $C_{17}H_{13}O_4N_5$ requires C, 58·2; H, 3·7%). Mixed with the above dinitrophenylhydrazone from 2 : 3-dimethylquinoline, the m. p. was depressed to 242—246°.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 29th,* 1949.]

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155. *Polarographic Reduction of Some Heterocyclic Molecules. Part I. The Reduction of Cinchoninic Acid.*

By D. J. CASIMIR and L. E. LYONS.

Cinchoninic acid is reduced at the dropping-mercury cathode over the pH range 1—13. The mechanism differs with the pH but in every case a total of two hydrogen ions and two electrons is used for each molecule. Waves with $n = 2$ occur in both extremes of pH, but around the neutral point the reduction proceeds in two separate stages, each involving one electron. As the slopes of the waves on logarithmic analysis do not give simple values the theory of van Rysselberghe has been tested but found to fail. Acid conditions are most suitable for the determination of cinchoninic acid.

THE polarographic reduction of quinoline-2- and -8-carboxylic acids has been studied by Stock (*J.*, 1944, 427; 1949, 586). The detailed mechanism still remains in some doubt. The behaviour of quinoline-4-carboxylic acid is now reported and discussed. All work was done on well-buffered aqueous solutions, at 25·0° generally, from pH 1 to pH 13; potentials are referred to the saturated calomel electrode at 25°. The concentration used was, unless otherwise specified, 2·00 × 10^{-3} M. The present work is part of a wider study which should complement that of Stock.

The reduction of cinchoninic acid gives waves over the entire pH range: at pH 1—8 a single wave, *A*, which at pH 8—11 is replaced by two waves, *B* and *C*, each half the height of *A*. At still higher pH's the curve is once more a single wave, *D*, similar to *A* in height. As the pH rises the reduction becomes more difficult and the curves are displaced to more negative potentials. Typical waves are shown in Fig. 1. The lowering of hydrogen overvoltage was observed, as is usual with quinoline derivatives (cf. Stock, *J.*, 1949, 763), but in this case was not sufficient to interfere with the reduction curve even at pH 1·3. In addition to the main waves pre-steps to *A* and *D* were observed (see below). Maxima were eliminated by the use of gelatin. These pre-steps occurred around pH 7 but only to a much less extent than with quinaldinic acid. Some minor aberrations from a smooth form were observed near the neutral point.

The half-wave potential, $E_{\frac{1}{2}}$, of wave *A* was a linear function of pH, and for pH <8 is given by $E_{\frac{1}{2}} = -(0{\cdot}550 + 0{\cdot}068\ \text{pH})$ volts. This same equation applies to $E_{\frac{1}{2}}$ of wave *B* when pH is >8. Fig. 2 shows $E_{\frac{1}{2}}$–pH relationships for all waves. $E_{\frac{1}{2}}$ of *C* and *D* appeared independent of pH.

The wave-heights when plotted against pH showed that waves *A* and *D* were of approximately constant height (11·1 µa.) for pH 1—8 and pH >11 respectively, while *B* and *C* were constant at 5·3 µa. for pH 8—11, for the given capillary characteristics. In order to compare one compound with another examined on a different set-up it is necessary to eliminate the latter factor; consequently, a plot of pH against the wave-height divided by $m^{2/3}t^{1/6}$ is shown in Fig. 3, the wave-height having been corrected for variations in residual current and in drop-time variation with electrode potential. It is suggested that such a plot should become standard in future polarographic studies rather than a plot of pH against wave-height in µa.

FIG. 1.

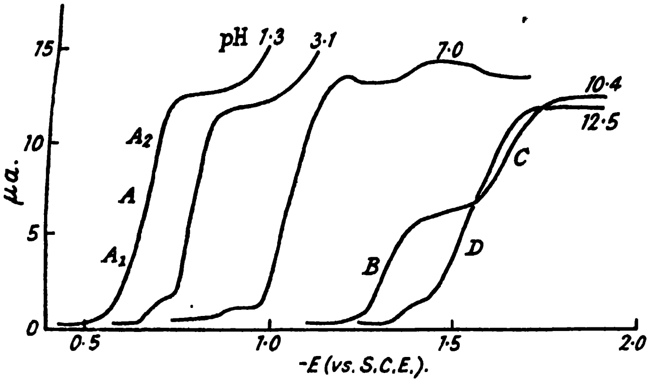


FIG. 2.

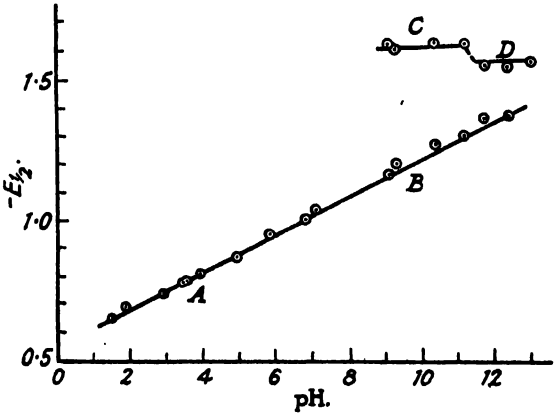
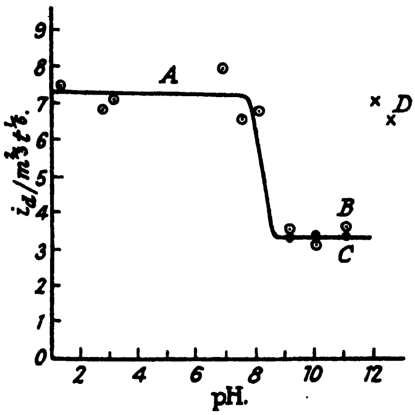


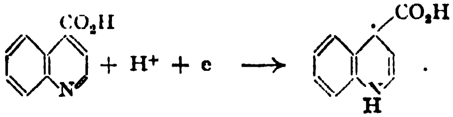
FIG. 3.



The number, *n*, of electrons per molecule concerned in the reduction process at each diffusion-controlled wave may be estimated from Ilkovic's equation $n = i_d/605D^{\frac{1}{2}}Cm^{2/3}t^{1/6}$, where i_d is the diffusion current in µa., *D* the diffusion coefficient in cm.^{2} sec.$^{-1}$, *C* the concentration of the reducible substance in millimoles/l., *m* the mg. of mercury dropping per second, and *t* the drop-time in seconds. Taking the value of *D* to be the same as that of quinaldinic acid, 0·80 × 10^{-5} cm.^{2} sec.$^{-1}$ (Stock, *loc. cit.*), the following (nearest integer) values were obtained: *A*, $n = 2$; *B*, $n = 1$; C, $n = 1$; *D*, $n = 2$. With the reverse procedure, assuming the value of *n* to be exactly either 2 or 1, the mean value of the diffusion coefficient was 0·88 (±0·04) × 10^{-5} cm.^{2} sec.$^{-1}$, to be compared with quinoline-2-carboxylic acid 0·80 × 10^{-5} (from conductivity data), quinoline-8-carboxylic acid 0·92 × 10^{-5}, and 8-hydroxyquinoline 0·85 × 10^{-5} (both from polarography).

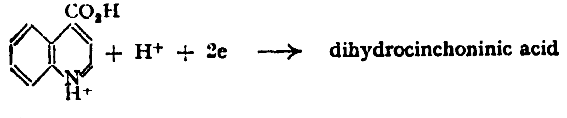
The plots of log $i/(i_d - i)$ against *E* were generally linear for *E* near $E_{\frac{1}{2}}$, but the slopes varied from curve to curve. Thus for wave *A* slopes of 0·062, 0·070, 0·079, 0·082, 0·084, and 0·086 were obtained. Exclusion of a section of wave *A* which seemed possibly to overlie a pre-step lowered these values, *e.g.*, from 0·062 to 0·051. For a two-electron process the corresponding slope for a "reversible" reaction equals 0·030, and for a one-electron process 0·059. The discrepancy between 0·030 and the observed values might, it was thought, be explicable by the theory of van Rysselberghe (*J. Amer. Chem. Soc.*, 1946, **68**, 2047). This theory attempts to explain the departure of certain polarographic curves from the reversible reaction slope in terms of a Freundlich adsorption isotherm for the product of the electrode reaction. The theory is not applicable if the half-wave potential varies markedly with either temperature or concentration of the reducible substance. For cinchoninic acid, experimentally $E_{\frac{1}{2}} = 0{\cdot}795$ v. at 25°, 0·787 v. at 35°, and 0·793 v. at 45° (all compared to S.C.E. at 25°; $c = 2{\cdot}00 \times 10^{-3}$ M.; pH 3·55). Also $E_{\frac{1}{2}} = 0{\cdot}795$ v. for $2{\cdot}00 \times 10^{-3}$ M., and 0·792 v. for $1{\cdot}00 \times 10^{-3}$ M. (25°; pH 3·55). The value of $E_{\frac{1}{2}}$ in every case was obtained from a curve which had been corrected for residual current (cf. Delahay, *Rec. Trav. chim.*, 1948, **67**, 159) and for the iR drop across the cell (R being measured each time using A.C.). Thus the van Rysselberghe theory might be thought applicable. Under our conditions the theory gives rise to the relation $dE/di = 0{\cdot}051x$, where x = the number of molecules which react with two hydrogen ions and two electrons. The number of electrons reacting with each molecule reduced is thus $2/x$. Measurement of dE/di for wave A gave x values in eleven different cases ranging from 1·8 to 3·6 with an average of 2·6. It follows that n obtained from the Ilkovic equation differs from that obtained from the van Rysselberghe theory by a factor of more than two. Thus the theory seems not to be of general applicability.

The variation in ultra-violet absorption spectrum with pH has been studied for quinaldinic acid (Lyons, *Proc. Roy. Soc. N.S.W.*, in the press), the polarography of which resembles that of cinchoninic acid. From this and other evidence there is no doubt that at pH $\leqslant 4$ the latter is present in the form containing H^+ on the nitrogen atom. Further evidence may be obtained from the polarography of 8-hydroxyquinoline (Stock, *loc. cit.*), where the $E_{\frac{1}{2}}$-pH plot of (Stock's) wave B shows an inflection at pH 5·3, although his larger wave A, which may be considered analogous to A of the present paper, shows no such inflection. Casimir and Lyons (unpublished) obtained such an inflection for quinoline itself, but here wave A seems to correspond to a one-electron process (resembling 8-hydroxyquinoline but not the 2- or 4-carboxylic acids). All this, and the fact that the $E_{\frac{1}{2}}$-pH plot (Fig. 2) for cinchoninic acid shows no inflection about pH 5, means that the first half (A_1) of A may *not* be identified in origin with B which is attributable to

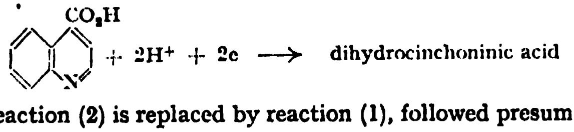


. . . . (1)

But to connect A_1 with the addition of only a single electron to $\equiv NH^+$ as the potential-determining step is not valid as the half-wave potential of A_1 varies with pH. All that can be done at the present stage of theory is to associate the whole wave A with reaction (2*a*) when pH $<$ pK, and with reaction (2*b*) when pH $>$ p$K < 8$ ($K \equiv$ dissociation constant of the base).

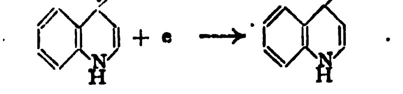


. . . . (2*a*)



. . . . (2*b*)

For pH $> 8 < 11$ reaction (2) is replaced by reaction (1), followed presumably by



. . . . (3)

which may then react with water to give the dihydro-compound. It may be possible to verify reaction (3) by theoretical calculations after the method of Maccoll (*Nature*, 1949, **163**, 178). Reaction (3) may be associated with wave C. The fact that $E_{\frac{1}{2}}$ of C is independent of pH supports the mechanism.

For pH >11 the potential-determining step must consist solely of the addition of two electrons, in order that $E_{\frac{1}{2}}$ of D be independent of pH, the product ion reacting to give the dihydro-compound. In each instance formation of the latter would be followed by di- or tri-merisation.

Comparative data (see table) for the first main wave of certain quinoline derivatives of quinoline show that a similar mechanism to the above may apply to quinoline-2- (Stock) and -4-carboxylic acid and 8-hydroxyquinoline (Stock), but not to quinoline-8-carboxylic acid (Stock) or to quinaldine or quinoline itself (Casimir and Lyons, unpublished).

Data for the first main wave of quinoline derivatives.

Derivative:	2-CH$_3$.	2-CO$_2$H.	4-CO$_2$H.	8-CO$_2$H.	8-OH.
n.	1.	2.	2.	1.	2.
$E_{\frac{1}{2}}$ at pH 0	0·52	0·52	0·59	0·78	0·95
$E_{\frac{1}{2}}$–pH slope	0·066	0·060	0·061	0·060	0·042

It is suggested that $E_{\frac{1}{2}}$ at pH 0 values, together with *n* values, might serve to distinguish the various compounds analytically. The best conditions for straightforward polarographic analysis exist in solutions of pH <3 where the wave is single and $E_{\frac{1}{2}}$ least negative.

Pre-steps were observed with both the waves *A* and *D* and in both cases occurred at potentials mostly independent of pH. [That to *A* occurred at 0·67 v. (pH 1·3 and 3·1); that to *D* at 1·36 v. (pH 11·8), 1·35 v. (pH 12·5), but 1·21 v. (pH 10·4).] The pre-step to *A* indicates adsorption of the ion, and that to *D* adsorption of the free base on the surface of the mercury drop (cf. Brolička, *Z. Elektrochem.*, 1942, **48**, 278), with the energy of adsorption utilised in the reduction process.

EXPERIMENTAL.

Buffer solutions used were made from the following solutions: pH 1·3 and 2·1: 0·2N-KCl–0·2N-HCl; pH 3·1 and 4·0: 0·05M-borax–0·05M-succinic acid; pH 4·9: 0·1N-NaOH–0·1M-potassium hydrogen phthalate; pH 5·9 and 7·0: 0·1N-NaOH–0·1M-KH$_2$PO$_4$; pH 7·2: 0·05M-borax–0·2M-H$_3$BO$_3$; pH 8·2, 10·3, 10·6, 11·1, 11·7, and 12·4: 0·1N-NaOH–0·1N-NaCl–0·1M-glycine; pH 8·8 and 9·0: 0·1N-NaOH–0·1M-H$_3$BO$_3$. The cinchoninic acid (m. p. 252—253°) was prepared by H. C. Freeman, whom the authors thank. The apparatus of conventional design was manually controlled. The cell was connected by an agar–saturated potassium chloride bridge to a saturated calomel electrode, all in a thermostat keeping the temperature within ±0·01°. Purified hydrogen was used to remove dissolved oxygen. The characteristics of the capillary used for most of the work were $m = 1·24$ mg./sec.; $t = 5·66$ sec. (closed circuit; pH 3·08); ($m^{2/3}t^{1/6} = 1·55$).

The 50-Ω coil resistance galvanometer was shunted and calibrated with a standard meter in series.

THE UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA.
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156. cyclo*Hexylidene Derivatives of Mannitol.*

By E. J. BOURNE, W. M. CORBETT, and D. ERILINNE.

Concentrated acids catalyse the formation of *tri*cyclo*hexylidene mannitol* from mannitol and *cyclo*hexanone. Hydrolysis of the tri*cyclo*hexylidene compound affords a *di-* and a *mono-*cyclo*hexylidene mannitol.* Conclusive evidence is presented to show that these compounds are, respectively, the 1 : 2-3 : 4-5 : 6-, 1 : 2-3 : 4-, and 3 : 4-*cyclo*hexylidene derivatives.

As part of a wider study of the various cyclic structures which result from the condensation of hexitols with aldehydes and ketones, we have examined *tri*cyclo*hexylidene mannitol,* and have obtained unequivocal proof that the three *cyclo*hexylidene residues in this compound are attached to the 1 : 2-, 3 : 4-, and 5 : 6-positions, respectively. Thus, it is a five-membered-ring structure which is favoured in each case. We believe this to be the first occasion on which the synthesis of a *cyclo*hexylidene derivative of a hexitol has been reported.

Tri*cyclo*hexylidene mannitol was obtained as long needles when commercial D-mannitol was shaken with *cyclo*hexanone in the presence of concentrated hydrobromic or 5N-hydrochloric acid. Since dilute aqueous acid normally favours the hydrolysis of cyclic acetals, it is probable that the high proportion of the tri*cyclo*hexylidene compound present at equilibrium can be attributed to its extremely small solubility in water. When a solution of tri*cyclo*hexylidene mannitol in hot aqueous alcohol was treated with hydrochloric acid, mannitol was regenerated, an observation which clearly showed that the new compound could not have arisen from the impurities known to contaminate hexitols prepared industrially (see Bourne and Wiggins, *J.*, 1948, 1933).

Graded hydrolysis of tri*cyclo*hexylidene mannitol with aqueous hydrochloric acid in alcohol–dioxan gave a crystalline *di-* and a syrupy *mono-*cyclo*hexylidene mannitol,* together with a small amount of mannitol. The products were separated by virtue of their relative solubilities in water, acetone, and alcohol. On appropriate treatment the mono- or the di-*cyclo*hexylidene compound regenerated the tri*cyclo*hexylidene derivative.

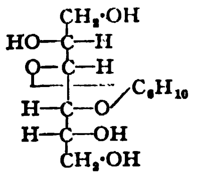
The presence of four free alcohol groups in the mono*cyclo*hexylidene mannitol was demonstrated by its conversion into three crystalline esters, namely the *tetra-acetate*, the *tetrabenzoate*, and the *tetratoluene*-p-*sulphonate*. Catalytic deacetylation of the tetra-acetate afforded a syrup whose properties were very similar to those of the original mono*cyclo*hexylidene mannitol. This fact, together with the observation that chromatography on alumina yielded only one component, indicated that the syrupy mono*cyclo*hexylidene mannitol was not a mixture.

Proof that the *cyclo*hexylidene residue bridged positions 3 and 4 as in (I), was obtained from two different lines of approach, one involving synthesis and the other oxidative degradation. First, the well-known 1 : 2 : 5 : 6-tetrabenzoyl mannitol, prepared by Fischer (*Ber.*, 1915, **48**, 266) from 3 : 4-*iso*propylidene mannitol, was converted, by treatment with *cyclo*hexanone and hydrobromic acid, into a crystalline tetrabenzoyl mono*cyclo*hexylidene mannitol, identical with that already prepared from the syrupy mono*cyclo*hexylidene compound by benzoylation. The structures of 1 : 2 : 5 : 6-tetrabenzoyl mannitol and of the parent 3 : 4-*iso*propylidene mannitol have been well authenticated (see, *e.g.*, *Ber.*, 1932, **65**, 1055; 1933, **66**, 931, and *Helv. Chim. Acta*, 1934, **17**, 1574) and it follows that, unless acyl migration had occurred, our product was 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene mannitol.

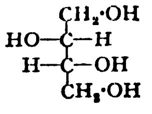
Secondly, 2 atomic proportions of oxygen were taken up when mono*cyclo*hexylidene mannitol was oxidised with either lead tetra-acetate or sodium metaperiodate. The formaldehyde liberated was isolated, as its dimedone compound, in sufficient quantity to prove that two glycol groups occupied terminal positions in the mannitol molecule. Furthermore, the larger moiety resulting from the oxidation gave rise, by hydrolysis and catalytic hydrogenation, to D-threitol (II), identified as its crystalline dibenzylidene derivative. Thus the possibility of the *cyclo*hexanone residue spanning any positions other than 3 and 4 cannot be entertained.

Such a structure, possessing two unsubstituted primary alcohol groups, explains the ready formation of a ditrityl derivative (cf. Helferich, *Advances in Carbohydrate Chem.*, 1948, Vol. 3, p. 88). Furthermore, since the tetratoluene-*p*-sulphonate would have contiguous ester groups at positions 1 : 2 and 5 : 6, it can be seen why almost four moles of sodium toluene-*p*-sulphonate were formed when this ester was treated with sodium iodide in dry acetone (cf. Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73).

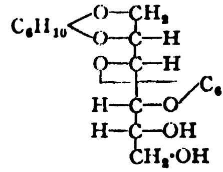
Attention was now directed to the di*cyclo*hexylidene mannitol, in which two free alcohol groups were detected by the isolation of a syrupy *diacetate* and a syrupy *dibenzoate*. Since the di*cyclo*hexylidene compound consumed one atomic proportion of oxygen and gave one molecular proportion of formaldehyde when treated with lead tetra-acetate or sodium metaperiodate, these hydroxy-groupings constituted a terminal α-glycol group. Consequently, the compound under examination was the 1 : 2 : 3 : 4-derivative, for the stereochemistry of mannitol obviates any necessity to distinguish between the 1 : 2- and the 5 : 6-positions. The larger fragment arising from the oxidative scission should then be a *di*cyclo*hexylidene* aldehydo-D-*arabinose*, and a syrup which analysed correctly for this compound was in fact isolated. When hydrolysed with acid, it afforded D-arabinose, which was converted into D-arabinosazone.



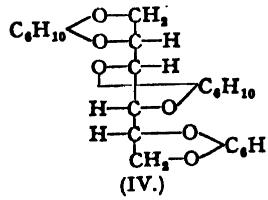
(I.)



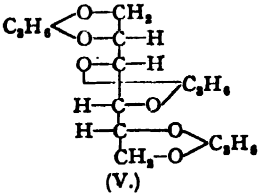
(II.)



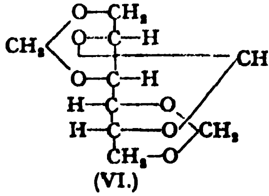
(III.)



(IV.)



(V.)



(VI.)

Regarding the finer structure of di*cyclo*hexylidene mannitol, three possibilities remained, *viz.*: the 1 : 2-3 : 4-, the 1 : 3-2 : 4-, and the 1 : 4-2 : 3-derivative. However, graded hydrolysis and subsequent benzoylation yielded 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene D-mannitol, identical with the material already prepared by two different routes, thus eliminating all but the first possibility (III). Since the mono- and di-*cyclo*hexylidene mannitols had been derived from tri*cyclo*hexylidene mannitol, the last must have been the 1 : 2-3 : 4-5 : 6-compound (IV).

The general pattern in the tri*cyclo*hexylidene mannitol molecule is thus the same as that in tri*iso*propylidene mannitol (V) (Wiggins, *J.*, 1946, 13), but different from that in trimethylene mannitol (VI) (Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, 65, 2215). In both the *cyclo*hexylidene and the *iso*propylidene series, it is the 3 : 4-derivative which is most stable under acid conditions. It is noteworthy that *cyclo*hexanone and acetone are similar also in their reactions with glucose, the 1 : 2-5 : 6-derivative being produced in each case (Hockett, Miller, and Scattergood, *J. Amer. Chem. Soc.*, 1949, 71, 3072).

EXPERIMENTAL.

Attempts to purify by distillation, in a high vacuum, the syrupy *cyclo*hexylidene compounds mentioned below invariably resulted in their decomposition.

1 : 2-3 : 4-5 : 6-*Tri*cyclo*hexylidene* D-*Mannitol from Mannitol*.—Commercial mannitol (50 g.), *cyclo*hexanone (106 c.c.), and hydrobromic acid (1·25 l.; *d* 1·4) were shaken together for 20 hours and then poured into ice-water. The precipitated 1 : 2-3 : 4-5 : 6-*tri*cyclo*hexylidene* D-*mannitol* was separated by filtration, washed with dilute sodium hydroxide solution and then with water, and crystallised 3 times from alcohol in long needles (35 g.), m. p. 82·5—83·5°, $[\alpha]_D^{22}$ +15·4° (*c*, 1·24 in chloroform) [Found : C, 68·3; H, 9·25%; *M*, *ca.* 440 (Rast). $C_{24}H_{38}O_6$ requires C, 68·3; H, 9·1%; *M*, 422].

Mannitol Hexa-acetate from 1 : 2-3 : 4-5 : 6-*Tri*cyclo*hexylidene* D-*Mannitol*.—A solution of tri*cyclo*hexylidene mannitol (1·00 g.) in alcohol (36 c.c.) was heated with 2N-hydrochloric acid (24 c.c.) in a water-bath at 100° for 2 hours, before being diluted with water and extracted with ether to remove the *cyclo*hexanone produced. The residue obtained when the aqueous layer was evaporated at 60°/12 mm. was refluxed for 2 hours with acetic anhydride (8·0 c.c.) in the presence of fused sodium acetate (2 g.), poured into ice-water, and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$), and concentrated to a syrup, which crystallised from alcohol. Recrystallised from alcohol, the product (0·45 g.) had m. p. 123°, alone or on admixture with an authentic specimen of mannitol hexa-acetate

Graded Hydrolysis of 1 : 2-3 : 4-5 : 6-*Tri*cyclo*hexylidene* D-*Mannitol*.—A suspension of tri*cyclo*hexylidene mannitol (45 g.) in a mixture of dioxan (230 c.c.), alcohol (100 c.c.), and 5N-hydrochloric acid (70 c.c.) was kept at 35°, with occasional shaking, for 2 hours, by which time dissolution was complete. The solution was neutralised with lead carbonate, and the lead salts were removed by filtration before being washed with a little water and then with acetone. The filtrate and washings were combined and concentrated at 40°/12 mm. to a syrup, which was extracted several times with water. Trituration of the insoluble residue with acetone afforded tri*cyclo*hexylidene mannitol as needles (8·84 g.), m. p. and mixed m. p. 82·5°. The acetone-soluble fraction was crystallised once from aqueous alcohol and twice from light petroleum, giving 1 : 2-3 : 4-*di*cyclo*hexylidene* D-*mannitol* (8·62 g.), m. p. 52—54°, $[\alpha]_D^{20}$ +11·2° (*c*, 1·07 in chloroform) (Found : C, 63·1; H, 9·0. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·8%).

The combined aqueous extracts were concentrated to a clear syrup, which deposited crystals of mannitol (4·0 g.) (confirmed by acetylation) from absolute alcohol. Evaporation of the alcoholic mother-liquors left 3 : 4-cyclo*hexylidene* D-*mannitol* (10·0 g.) as a syrup which, when dried at 65°/0·05 mm. for 1 hour, had n_D^{25} 1·4925, $[\alpha]_D^{19}$ +17·4° (*c*, 1·99 in chloroform) (Found : C, 55·0; H, 8·4. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·5%).

1 : 2-3 : 4-5 : 6-*Tri*cyclo*hexylidene* D-*Mannitol from* 1 : 2-3 : 4-*Di*cyclo*hexylidene* D-*Mannitol*.—Di*cyclo*hexylidene mannitol (0·04 g.), *cyclo*hexanone (0·20 c.c.), and 5N-hydrochloric acid (3·0 c.c.) were shaken together for 30 minutes and the solid product was removed by filtration. After being washed with water, it recrystallised from aqueous alcohol in needles, m. p. 80—82°, alone or on admixture with 1 : 2-3 : 4-5 : 6-tri*cyclo*hexylidene mannitol prepared directly from mannitol.

1 : 2-3 : 4-5 : 6-*Tri*cyclo*hexylidene* D-*Mannitol from* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—3 : 4-*cyclo*-Hexylidene mannitol (0·50 g.), *cyclo*hexanone (0·70 c.c.), and 5N-hydrochloric acid (4·0 c.c.) were shaken together for 20 hours. The solid product was removed by filtration, washed with sodium hydrogen carbonate solution and then with water, and crystallised from aqueous alcohol in needles (0·39 g.), m. p. 82—83°, alone or on admixture with 1 : 2-3 : 4-5 : 6-tri*cyclo*hexylidene mannitol prepared directly from mannitol.

1 : 2 : 5 : 6-*Tetra-acetyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—3 : 4-*cyclo*Hexylidene mannitol (3·06 g.) was treated with pyridine (12·0 c.c.)–acetic anhydride (6·0 c.c.) for 48 hours at 18°. The oil which separated when the solution was poured into ice-water crystallised after several hours. Recrystallised 3 times from aqueous alcohol, the *acetate* (3·07 g.) had m. p. 67—68·5°, $[\alpha]_D^{20}$ +50·7° (*c*, 1·12 in chloroform) (Found : C, 55·5; H, 7·0; Ac, 39·1. $C_{20}H_{30}O_{10}$ requires C, 55·8; H, 7·0; Ac, 40·0%).

Regeneration of 3 : 4-cyclo*Hexylidene* D-*Mannitol from its Tetra-acetate*.—The tetra-acetate (0·552 g.) was treated for 48 hours with a trace of sodium in absolute methanol (10 c.c.). Carbon dioxide was bubbled through the solution, and the solvent was removed by distillation. The dry residue was extracted with chloroform. Concentration of the extracts afforded 3 : 4-*cyclo*hexylidene D-mannitol as a syrup (0·286 g.), n_D^{25} 1·4965, $[\alpha]_D^{20}$ +17·7° (*c*, 1·18 in chloroform).

1 : 2 : 5 : 6-*Tetrabenzoyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—Benzoyl chloride (1·50 c.c.) was added to a cooled solution of 3 : 4-*cyclo*hexylidene mannitol (0·659 g.) in pyridine (3·0 c.c.). After 18 hours at room temperature, the solution was poured into water and the precipitate collected. Three crystallisations from acetone–alcohol gave 1 : 2 : 5 : 6-*tetrabenzoyl* 3 : 4-cyclo*hexylidene* D-*mannitol*

(0·806 g.), m. p. 147·5—148·5°, $[\alpha]_D^{26}$ −7·7° (*c*, 1·16 in chloroform) (Found : C, 71·0; H, 5·8. $C_{40}H_{38}O_{10}$ requires C, 70·8; H, 5·65%).

1 : 2 : 5 : 6-*Tetratoluene*-p-*sulphonyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—3 : 4-*cyclo*Hexylidene mannitol (0·829 g.) was treated with toluene-*p*-sulphonyl chloride (2·66 g.) in pyridine (10 c.c.) at 35° for 72 hours, before being poured into ice-water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, dried ($MgSO_4$), filtered, and concentrated to a syrup, which crystallised from absolute alcohol. After 3 more crystallisations, the *product* (0·385 g.) had m. p. 135—137°, $[\alpha]_D^{23}$ +4·9° (*c*, 1·03 in chloroform) (Found : C, 54·9; H, 5·4; S, 14·0. $C_{40}H_{46}O_{14}S_4$ requires C, 54·7; H, 5·3; S, 14·6%).

Reaction of 1 : 2 : 5 : 6-*Tetratoluene*-p-*sulphonyl* 3 : 4-cyclo*Hexylidene* D-*Mannitol with Sodium Iodide in Acetone*.—The toluene-*p*-sulphonate (0·1007 g.) and sodium iodide (0·204 g.) were dissolved in dry acetone (15 c.c.) and heated in a sealed tube at 100—110° for 8 hours. The precipitated sodium toluene-*p*-sulphonate (0·0833 g.) represented an exchange of 3·75 ester groups per molecule.

1 : 6-*Ditrityl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—3 : 4-*cyclo*Hexylidene mannitol (0·350 g.) and triphenylmethyl chloride (0·745 g.) were dissolved in pyridine (3·0 c.c.) and kept at room temperature for 48 hours. The sticky solid ether (0·950 g.), which separated when the solution was poured into ice-water, could not be crystallised. It had $[\alpha]_D^{23}$ +12·5° (*c*, 1·12 in chloroform).

2 : 5-*Diacetyl* 1 : 6-*Ditrityl* 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—1 : 6-Ditrityl 3 : 4-*cyclo*hexylidene mannitol (0·706 g.) was dissolved in pyridine (2·0 c.c.) and acetic anhydride (0·5 c.c.) was added. After 18 hours, the mixture was poured into ice-water and extracted with chloroform. The extracts were washed with dilute acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), filtered, and evaporated. The residual solid, crystallised 3 times from acetone–alcohol–water, afforded 2 : 5-*diacetyl* 1 : 6-*ditrityl* 3 : 4-cyclo*hexylidene* D-*mannitol* (0·532 g.), m. p. 197—198°, $[\alpha]_D^{20}$ ±0·0° (*c*, 0·93 in chloroform) (Found : C, 78·0; H, 6·6. $C_{54}H_{54}O_8$ requires C, 78·0; H, 6·6%).

1 : 2 : 5 : 6-*Tetrabenzoyl* D-*Mannitol*.—Hydrolysis of 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*iso*propylidene D-mannitol (0·503 g.; m. p. 121°) by the method of Fischer (*loc. cit.*) gave 1 : 2 : 5 : 6-tetrabenzoyl D-mannitol (0·387 g.), m. p. 117—119°, $[\alpha]_D^{18}$ +7·9° (*c*, 1·3 in tetrachloroethane) (Found : C, 68·3; H, 5·2. Calc. for $C_{34}H_{30}O_{10}$: C, 68·2; H, 5·1%). Fischer (*loc. cit.*) gave m. p. 122—123°, $[\alpha]_D^{18}$ +7·83° in tetrachloroethane.

Treatment of 1 : 2 : 5 : 6-*Tetrabenzoyl* D-*Mannitol with* cyclo*Hexanone*.—The tetrabenzoate (0·050 g.), *cyclo*hexanone (2·0 c.c.), and hydrobromic acid (0·5 c.c.; *d* 1·4) were shaken together for 18 hours. The heavy oil, which separated when the reaction mixture was poured into ice-water, crystallised when triturated with alcohol. Recrystallisation from acetone–alcohol gave 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene D-mannitol (0·049 g.), m. p. 147·5—148·5° (alone or on admixture with the compound mentioned above), $[\alpha]_D^{25}$ −7·7° (*c*, 0·65 in chloroform).

Lead Tetra-acetate Oxidation of 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—Tetra-acetyl *cyclo*hexylidene mannitol ($3·93 \times 10^{-4}$ mole) was deacetylated with sodium in methanol, and the product was oxidised with lead tetra-acetate according to the procedure of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667). The number of g.-atoms of oxygen taken up per g.-mol. was 0·37 (10 minutes), 1·26 (60 minutes), 1·64 (120 minutes), 1·84 (180 minutes), and 1·98 (300 minutes).

Periodate Oxidation of 3 : 4-cyclo*Hexylidene* D-*Mannitol*.—(a) *Isolation of formaldehyde*. 3 : 4-*cyclo*Hexylidene mannitol ($0·4 \times 10^{-4}$ moles) was oxidised under the conditions recommended by Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476), and, in 4 hours, $0·673 \times 10^{-4}$ mole of formaldehyde, isolated as its dimedone derivative (m. p. 189°), was liberated. This represented 1·68 moles of formaldehyde per mole of *cyclo*hexylidene mannitol. Longer periods of oxidation resulted in somewhat lower yields of formaldehyde, presumably because this initial product was slowly oxidised to formic acid (cf. Hirst and Jones, *J.*, 1949, 1659).

(b) *Isolation of dibenzylidene* D-*threitol*. 3 : 4-*cyclo*Hexylidene mannitol (3·310 g.) was dissolved in the minimum volume of water and an aqueous solution (50 c.c.) of sodium metaperiodate (5·12 g.) was added. After 24 hours at room temperature, the solution was saturated with salt and extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and concentrated to a syrup (0·847 g.) which showed positive Schiff's and Fehling's tests and had n_D^{21} 1·4845, $[\alpha]_D^{20}$ (equilibrium) −23·1° (*c*, 1·17 in chloroform). This probably was 2 : 3-*cyclo*hexylidene D-*threo*dihydroxysuccinic dialdehyde.

The syrup (0·574 g.) was hydrolysed with N-sulphuric acid (12·5 c.c.) at 100° for 3 hours. The solution was neutralised with barium carbonate, filtered, and evaporated at 35°/12 mm. The residue was extracted with absolute methanol, and evaporation of the solution left a resinous residue (0·173 g.), which rapidly reduced Fehling's solution.

The D-*threo*dihydroxysuccinic dialdehyde was hydrogenated with Raney nickel in alcohol (50 c.c.) at 40°/30 atm. for 20 hours. The catalyst was removed by filtration and the filtrate was concentrated to a syrup, which was dissolved in absolute methanol (25 c.c.). The solution was saturated with dry hydrogen chloride, benzaldehyde (10 c.c.) was added, and the mixture was shaken for 20 hours, before being neutralised with sodium hydrogen carbonate and filtered. The filtrate was evaporated at 40°/12 mm. and the solid residue was extracted with chloroform. Removal of the solvent left a solid, which afforded dibenzylidene D-threitol (0·050 g.), m. p. 227°, $[\alpha]_D^{18}$ −94·5° (*c*, 0·275 in pyridine), when crystallised twice from alcohol and once from dioxan. Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 1663) give m. p. 231°, $[\alpha]_D^{20}$ −90·2° (*c*, 0·80 in pyridine), for dibenzylidene D-threitol.

5 : 6-*Diacetyl* 1 : 2-3 : 4-*Di*cyclo*hexylidene* D-*Mannitol*.—Di*cyclo*hexylidene mannitol (0·508 g.) was acetylated with acetic anhydride (1·10 c.c.) in pyridine (2·50 c.c.). After 20 hours, the solution was poured into ice-water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), filtered, and concentrated to a clear syrup, from which the last traces of solvent were removed at 65°/0·1 mm. The *product* (0·464 g.) had n_D^{21} 1·4798, $[\alpha]_D^{20}$ +24·9° (*c*, 1·33 in chloroform) (Found : C, 61·9; H, 8·3; Ac, 19·4. $C_{22}H_{34}O_8$ requires C, 61·9; H, 8·0; Ac, 20·2%).

5 : 6-*Dibenzoyl* 1 : 2-3 : 4-*Di*cyclo*hexylidene* D-*Mannitol*.—Di*cyclo*hexylidene mannitol (0·219 g.) was treated for 18 hours with benzoyl chloride (0·76 c.c.) in pyridine (1·5 c.c.) and then poured into ice-water.

The aqueous solution was extracted with chloroform. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. It was dried (Na_2SO_4), filtered, and evaporated to a syrup, from which all residual solvent was removed at 60°/0·05 mm. during 1 hour. The *product* (0·146 g.) showed $[\alpha]_D^{15}$ +7·4° (*c*, 1·1 in chloroform) and n_D^{18} 1·5475 (Found : C, 69·7; H, 6·9. $C_{32}H_{38}O_8$ requires C, 69·8; H, 7·0%).

Lead Tetra-acetate Oxidation of 1 : 2-3 : 4-*Di*cyclo*hexylidene* D-*Mannitol*.—When di*cyclo*hexylidene mannitol (4·83 × 10^{-4} moles) was oxidised with lead tetra-acetate, according to the method of Hockett and McClenahan (*loc. cit.*), the number of g.-atoms of oxygen taken up per g.-mol. was 0·46 (30 minutes), 0·56 (80 minutes), 0·78 (140 minutes), 0·88 (210 minutes), 0·95 (260 minutes), and 1·02 (320 minutes).

Periodate Oxidation of 1 : 2-3 : 4-*Di*cyclo*hexylidene* D-*Mannitol*.—(a) *Isolation of formaldehyde.* Di*cyclo*hexylidene mannitol, oxidised for 4 hours under the conditions recommended by Reeves (*loc. cit.*), gave, per mole, 1·04 moles of formaldehyde, isolated as its dimedone derivative (m. p. 189°).

(b) *Isolation of* 2 : 3-4 : 5-*di*cyclo*hexylidene* aldehydo-D-*arabinose*. Di*cyclo*hexylidene mannitol (1·00 g.) was dissolved in alcohol (3·0 c.c.), and water was added until there was a slight turbidity. Potassium metaperiodate (1·345 g.) was introduced and the mixture was shaken for 18 hours, before being saturated with sodium chloride and extracted with chloroform. The extract was dried (Na_2SO_4), filtered, and concentrated to a syrup, from which all the residual solvent was removed at 85°/0·005 mm. The *product* (0·78 g.), which restored the colour to decolorised magenta, had n_D^{27} 1·4890, $[\alpha]_D^{25}$ −5·3° (*c*, 0·94 in chloroform) (Found : C, 65·5; H, 8·6. $C_{17}H_{26}O_5$ requires C, 65·7; H, 8·4%).

(c) *Isolation of* D-*arabinose*. A portion of the di*cyclo*hexylidene *aldehydo*-D-arabinose (0·392 g.) was hydrolysed with N-sulphuric acid (7·5 c.c.) at 100° for 2 hours. The solution was neutralised with barium carbonate and filtered, and the filtrate concentrated at 35°, leaving a white solid. This was extracted with absolute methanol, from which crystals were deposited when the volume was reduced. Recrystallised from absolute methanol, the product (0·150 g.) had m. p. 158—159°, alone or on admixture with D-arabinose, $[\alpha]_D^{19}$ (equilibrium) −101·5° (*c*, 0·61 in water), compared with accepted values m. p. 159—160°, $[\alpha]_D^{20}$ (equilibrium) −104·5° (in water). With phenylhydrazine, under the usual conditions, it yielded D-arabinosazone, m. p. 162—163°.

3 : 4-cyclo*Hexylidene* D-*Mannitol from* 1 : 2-3 : 4-*Di*cyclo*hexylidene* D-*Mannitol*.—Di*cyclo*hexylidene D-mannitol (1·08 g.) was dissolved in alcohol (80 c.c.), and concentrated hydrochloric acid (20 c.c.) was added. After 150 minutes, the solution was neutralised with lead carbonate. The lead salts were removed by filtration and washed, first with a little water and then with acetone. The combined filtrate and washings were concentrated, the residue being extracted with water. The aqueous solution was evaporated, leaving a syrup, from which a little mannitol crystallised on trituration with acetone. Concentration of the acetone solution yielded a syrup, which was treated for 48 hours with benzoyl chloride (0·75 c.c.) in pyridine (1·50 c.c.). The product was precipitated with alcohol. Recrystallisation from acetone–alcohol gave 1 : 2 : 5 : 6-tetrabenzoyl 3 : 4-*cyclo*hexylidene D-mannitol (0·443 g.), m. p. 147·5—148·5°, alone or on admixture with either of the compounds mentioned above.

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THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15.
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157. *The Manganohalides of Pyridine.*

By W. S. Fyfe.

Dipyridinomanganous chloride combines with dry hydrogen chloride to form a green compound, previously formulated as $(PyH)_2MnCl_4$ and here reformulated as $H_2MnPy_2Cl_4$. The double salt $MnCl_2,PyHCl,H_2O$ has also been reformulated as the acid $H_2MnPyCl_3(OH)$. The potassium salts of these acids have been isolated.

A NUMBER of compounds of pyridine and manganous chloride have been described previously. Pincussohn (*Z. anorg. Chem.*, 1897, **14**, 388) gave details of a yellow compound, $MnCl_2,2PyHCl$, and a pink compound, $MnCl_2,PyHCl$, whilst Reitzenstein (*ibid.*, 1898, **18**, 290) described a green compound, $MnPy_2Cl_4$, and a pink salt, $MnPy_2Cl_2$. Meyer and Best (*ibid.*, 1900, **22**, 182) described the bromide, $MnBr_2,2PyHBr$. Taylor (*J.*, 1934, 699) revised this work and came to the following conclusions : (*a*) Pincussohn's yellow compound and Reitzenstein's green compound were identical and best formulated as $(PyH)_2MnCl_4$; (*b*) Pincussohn's pink compound was $MnCl_2,PyHCl,H_2O$; (*c*) Reitzenstein had reported that when the green compound, $MnPy_2Cl_4$, was pressed between filter papers the pink compound, $MnPy_2Cl_2$, was produced, chlorine being evolved in the change. Taylor proved that no loss of chlorine occurred and that the product was $MnCl_2,PyHCl,H_2O$; (*d*) the green colour of concentrated solutions was due to the $MnCl_4^{--}$ ion and the pink colour of more dilute solutions was due to the $(MnCl_3,H_2O)^{--}$ ion.

The present investigation indicates that, in the case of the green complex, the pyridine is bound to the manganese atom and is not present as the pyridinium ion. This compound has been reformulated as the complex dibasic acid, $H_2MnPy_2Cl_4$. The

compound, $MnCl_2,PyHCl,H_2O$, described by Taylor, has also been reformulated as the acid, $H_2MnPyCl_3(OH)$. The identity of the pink salt, $MnPy_2Cl_2$, described by Reitzenstein has been confirmed, and a new salt, $MnPy_2Cl_2,2H_2O$, described.

EXPERIMENTAL.

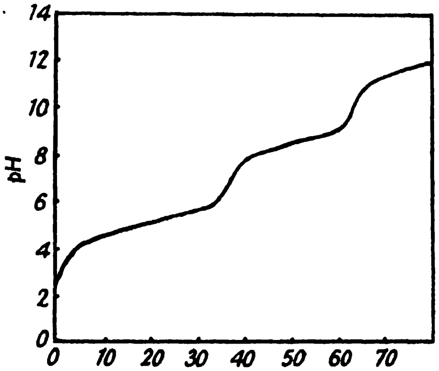
Dipyridinomanganous Chloride.—This compound is precipitated as fine pink needles on addition of pyridine to alcoholic solutions of manganous chloride. These can be washed in ether, vacuum dried, and recrystallised from alcohol (Found: Mn, 19·1; Cl, 25·2; N, 8·3. Calc. for $MnPy_2Cl_2$: Mn, 19·4; Cl, 25·0; N, 9·9%). Addition of pyridine to concentrated aqueous solutions of manganous chloride also precipitates this compound, which is also obtained when pyridine is added to a hot solution of manganous chloride in concentrated hydrochloric acid, but it then redissolves to form the green complex, $H_2MnPy_2Cl_4$.

All the chloride ions are precipitated in the cold by silver nitrate. The molar conductivities measured at 25° were:

Molar concentration	0·1	0·01	0·005	0·0025	0·0012
Conductivity (mhos)	164	191	216	250	280

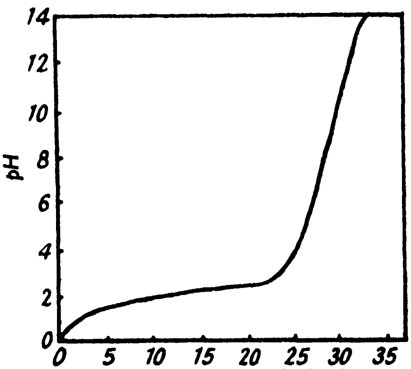
These measurements are in harmony with complete ionisation into $MnPy_2^{++}$ and $2Cl^-$. Freezing-point depressions in water gave a value of 68 for the molecular weight (Calc. for $MnPy_2Cl_2$: 284), *i.e.*, a van't Hoff's factor (*i*) of 4·2, indicating that the complex ion, $MnPy_2^{++}$, is also partly dissociated.

FIG. 1.



Neutralisation curve of 20 *c.c. of* 0·1M-$H_2MnPy_2Cl_4$.

FIG. 2.



Neutralisation curve of 15 *c.c. of* 5M-$H_2MnPy_2Cl_4$.

Dipyridinomanganous Chloride Dihydrate.—This compound crystallises in large white crystals from dilute solutions of manganous chloride and pyridine, and was originally found in the residues remaining after the crystallisation of $MnPy_2Cl_2$ (Found: Mn, 16·9; Cl, 22·1. $MnPy_2Cl_2,2H_2O$ requires Mn, 17·2; Cl, 22·2%). The *dihydrate* loses the two molecules of water on continued vacuum desiccation. It is not deliquescent but is readily soluble in water. Freezing-point and conductivity data are identical with those obtained for $MnPy_2Cl_2$, indicating that in solution the states of dipyridinomanganous chloride and its dihydrate are probably identical.

Hydrogen Tetrachlorodipyridinomanganate(II).—(*a*) This compound was prepared by Reitzenstein's method of adding pyridine to a solution of manganese dioxide in hydrochloric acid. On evaporation to dryness on a water-bath the green compound was obtained.

(*b*) The compound was similarly prepared from manganic oxide and trimanganese tetroxide.

(*c*) It can also be prepared by evaporating to dryness a solution of manganous chloride in hydrochloric acid and pyridine. Pale green crystals are obtained, and this material was used in physical measurements.

(*d*) The green material was also prepared by passing dry hydrogen chloride over dipyridinomanganous chloride, this change occurring very rapidly; the dihydrate does not change under these conditions.

Examination of the compounds, prepared in these different ways, by both analytical and optical methods indicated their identity (Found: Mn, 15·3; Cl, 39·6; N, 7·2. Calc. for $H_2MnPy_2Cl_4$: Mn, 15·4; Cl, 39·7; N, 7·8%). The apparent optic axial angle is 59° ± 2°; n_β 1·653 ± 0·002.

The material was purified by boiling in ether and chloroform, to remove traces of hydrogen chloride and pyridine hydrochloride. Recrystallisation from alcohol and water is not possible, and recrystallisation from pyridine produces dipyridinomanganous chloride, a change which gives some indication of the strength with which the hydrogen chloride is held in the lattice. The material was dried at about 1 mm.

A typical neutralisation curve for the complex is given in Fig. 1. In dilute solution a two-stage curve is obtained, the first stage corresponding to the neutralisation of the pyridinium ion and the second to the precipitation of manganous hydroxide. However, in concentrated solutions a one-stage curve, corresponding to the neutralisation of the acid, $H_2MnPy_2Cl_4$, is given (Fig. 2). In dilute solutions this material is extensively hydrolysed. Freezing-point depressions in aqueous solutions gave a value of 80 for the molecular weight (Calc. for $H_2MnPy_2Cl_4$: 357). This gives a value for *i* of 4·4. Molar conductivities measured at 20° were :

Molar concentration	5	0·5	0·1	0·01	0·001
Conductivity (mhos)	7	117	186	220	260

Preparation of $H_2MnPy_2Cl_4$ *from Manganese Dioxide and Manganous Chloride.*—Manganese dioxide dissolved in hydrochloric acid, in the presence of pyridine at 0°, formed at first a deep green solution and only slight amounts of chlorine were evolved even on warming the solution on a water-bath. It thus appeared that the deep green solution contained a complex ion of quadrivalent manganese. When the solution was evaporated to crystallisation little chlorine was evolved until near the crystallisation point when chlorine was liberated quantitatively: $MnO_2 + 4HCl = MnCl_2 + Cl_2 + 2H_2O$. At this stage the solution became a pale green and pale green crystals separated. The preparation of the green complex from manganous chloride was also studied, and no oxygen absorption, as occurs in the oxidation of the cobaltous amines, or hydrogen evolution was observed. It thus appears that the complex could not be other than one of the manganous ion.

Potassium Tetrachlorodipyridinomanganate(II).—This pink *salt* was precipitated when a green, concentrated solution of the acid was neutralised with concentrated potassium hydroxide. It is fairly soluble in water. If dilute solutions of the acid are used manganous hydroxide is precipitated (Found : Mn, 12·4; Cl, 33·0; Py, 38·0; K, 16·2. $K_2MnPy_2Cl_4$ requires Mn, 12·6; Cl, 32·8; Py, 36·6; K, 18·0%). The isolation of this material indicates that the green complex contains the $MnPy_2Cl_4^{--}$ ion.

Hydrogen Trichlorohydroxopyridinomanganate(II).—This compound was prepared by Reitzenstein by pressing the green complex between filter papers, and was erroneously recorded by him as $MnPy_2Cl_2$. It crystallises from dilute aqueous solutions of $H_2MnPy_2Cl_4$; pink crystals are obtained which can be washed in ether and chloroform. The *compound* crystallises as the monohydrate, and this molecule of water is lost on vacuum desiccation [Found, in vacuum-desiccated material: Mn, 21·1; Cl, 41·0. $H_2MnPyCl_3(OH)$ requires Mn, 21·1; Cl, 41·0%. Found in air-dried material: Mn, 19·5; Cl, 38·4. Calc. for $H_2MnPyCl_3(OH),H_2O$: Mn, 19·9; Cl, 38·6%]. It undergoes hydrolysis in dilute solutions as does $H_2MnPy_2Cl_4$, and repeated recrystallisations from water produce manganous chloride. By neutralising concentrated solutions of the pink acid with concentrated potassium hydroxide the potassium salt, $K_2MnPyCl_3(OH)$, was obtained.

In this series of compounds there is a steady drop in the β refractive index : $H_2MnPy_2Cl_4$, n_β 1·653; $H_2MnPyCl_3(OH)$, n_β 1·62; $MnCl_2,2H_2O$, n_β 1·59.

Ionic Migration Experiments.—These were conducted on a large number of the coloured solutions to obtained evidence as to whether the colour was in the anion or the cation. In the deep green solution from manganese dioxide in hydrochloric acid and pyridine and from manganous chloride in hydrochloric acid, and solutions of $H_2MnPy_2Cl_4$ the colour was associated with the anion.

Hydrogen Hexachlorodipyridinomanganate(IV).—The deep green solutions obtained at first from the solution of manganese dioxide in hydrochloric acid in the presence of pyridine most probably contain the quadrivalent complex acid, $H_2MnPy_2Cl_6$. This compound has been obtained in an impure condition by dissolving manganese dioxide in an ethereal solution of hydrogen chloride and pyridine. It separates as a green viscous liquid. All attempts to crystallise the material have led to its decomposition, and the formation of $H_2MnPy_2Cl_4$.

Nitrogen could not be determined satisfactorily by the Kjeldahl method; the method used was to steam-distil the pyridine from a strongly alkaline solution of the complex, and titrate the pyridine with hydrochloric acid, using a pH-meter.

DISCUSSION.

There is no doubt that Reitzenstein's formulation of the green complex as $MnPy_2Cl_4$ is incorrect; the compound does not contain quadrivalent manganese. Taylor formulated this complex as a pyridinium salt and doubtless much of the evidence from dilute solutions supports this view as the pyridinium ion is a product of the hydrolysis of the $MnPy_2Cl_4^{--}$ ion. However, the isolation of the alkali-metal salts supports the formulation of the green complex as the acid, $H_2MnPy_2Cl_4$. The very rapid entry of hydrogen chloride into the complex $MnPy_2Cl_2$ to form $H_2MnPy_2Cl_4$ when the gas is passed over the material, and its equally ready removal by washing it with pyridine, suggests that the hydrogen chloride molecule is co-ordinated and not taking part in the formation of a pyridinium ion. The addition of hydrogen chloride resembles the change of $PtCl_4$ to H_2PtCl_6 in which two molecules of hydrogen chloride are co-ordinately bound. This compound also is hydrolysed in water, losing hydrochloric acid. The complex dipyridinomanganous chloride contains two molecules of pyridine co-ordinated by the lone pair on the nitrogen to the manganese. The formation of the pyridinium salt $(PyH)_2MnCl_4$ by molecular rearrangement on exposure of the salt to hydrogen chloride would be improbable. Moreover, the hydrogen chloride is easily removed by treating the compound with pyridine. It is more probable that the chlorine atoms on the hydrogen chloride molecules fill up the remaining spaces in the lattice, donating their lone pairs and giving the manganous ion six-fold co-ordination. Freezing-point depressions do not support the presence of a three-ion salt and the stability in Kjeldahl nitrogen determinations is not to be expected from a pyridinium salt.

Two different structures have been proposed for dipyridinomanganous chloride; Cox, Shorter, Wardlaw, and Way (*J.*, 1937, 1556) concluded that the structure was similar to that of dipyridinocobaltous chloride, which has a *trans*-planar configuration. Mellor and Coryell (*J. Amer. Chem. Soc.*, 1938, 60, 1786) proposed an octahedral configuration from magnetic evidence. As the maximum co-ordination number of the manganous ion is six, it is not obvious, on the latter hypothesis, how water and hydrogen chloride could enter the lattice to give $MnPy_2Cl_2,2H_2O$ and $H_2MnPy_2Cl_4$.

Assuming the planar configuration, however, this addition could readily occur with the production of an octahedral configuration. It is noteworthy that hydrogen chloride has no effect on $MnPy_2Cl_2,2H_2O$, probably because there are no positions of entry for this molecule.

The instability of the green liquid, $H_2MnPy_2Cl_6$, is not unexpected on structural grounds, for in this compound the small quadrivalent manganese ion is in eight co-ordination.

Some evidence of the hydrolysis of the green acid in dilute solutions comes from the formation of the compounds $H_2MnPyCl_3(OH)$ and eventually $MnCl_2,2H_2O$ on continued recrystallisation. The change is essentially H–OH for H–Cl as occurs in the case of the platinic acids. As the complex ion is considerably dissociated the hydrogen chloride liberated will combine with any free pyridine from the dissociation $MnPy_2Cl_4^{--} = MnCl_4^{--} + 2Py$. The position of the pyridine molecule will then be taken by a water molecule. This change evidently at first goes only one stage, for $H_2MnPyCl_3(OH)$ can be isolated. A general scheme for the hydrolysis is:

$$H_2MnPy_2Cl_4 + 2HOH \longrightarrow H_2MnPyCl_3(OH),H_2O + PyHCl$$
$$H_2MnPyCl_3(OH),H_2O + 2H_2O \longrightarrow MnCl_2,4H_2O + PyHCl$$

The hydrolysis products and not the parent ions account for the properties of the dilute solutions. The freezing-point depressions indicate that in all cases the complex ions are considerably dissociated. Again the precipitation of the manganese ion by phosphate indicates that a considerable amount of the ion is present at equilibrium. The chloride ions are also readily precipitated from all the complexes. Magnetic measurements (Selwood, "Magnetochemistry," p. 153, Interscience Publishers, N.Y., 1943) show that all the complexes are paramagnetic and that no coupling of electrons has occurred; they are thus *normal* complexes on the Biltz classification. This is in agreement with their instability.

The author thanks Professor F. G. Soper for his advice and helpful criticism.

UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, August 15th, 1949.*]

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158. *Studies in Molecular Rearrangement. Part II.* Oxotropic Rearrangements in the Polycyclic Aromatic Series.*

By E. A. BRAUDE, J. S. FAWCETT, and D. D. E. NEWMAN.

The 1-aryl-3-methylallyl alcohols (I), where X = 1-naphthyl, 2-naphthyl, 9-anthryl, and 9-phenanthryl, have been prepared. They readily undergo the expected oxotropic rearrangements in the presence of dilute acids to give the corresponding 3-aryl-1-methylallyl alcohols (II). The structure of the latter was proved by Oppenauer oxidation to the ketones (III)

X·CH(OH)·CH:CHMe (I.) ⟶ X·CH:CH·CH(OH)Me (II.) ⟶ X·CH:CH·COMe (III.)

which were also obtained by condensation of the appropriate aryl aldehydes with acetone. The various derivatives have been characterised by their ultra-violet light-absorption properties which exhibit a number of interesting features.

IN two earlier papers (Braude, Jones, and Stern, *J.*, 1946, 396; 1947, 1087) the oxotropic rearrangements of phenylpropenylcarbinol (I; X = Ph) and of a number of nuclear-substituted phenylpropenylcarbinols (I; $X = C_6H_4R$) to the corresponding styrylmethylcarbinols (II) have been described. The rearrangements take place very readily in the presence of dilute acids, and at room temperature proceed either to completion or to equilibrium mixtures containing more than 90% of the conjugated isomers (II), as would be expected since the latter are stabilised by the considerable additional resonance energy of the styryl or substituted styryl system (Braude and Stern, *J.*, 1947, 1096). It was of interest to extend the range of this reaction to polycyclic aromatic derivatives in order to obtain some evidence concerning the conjugating properties of polycyclic aromatic groups. Moreover, a kinetic study of such rearrangements and a comparison with the data for phenylpropenylcarbinol would provide some quantitative information, which has been almost entirely lacking hitherto, regarding the effects of polycyclic aryl groups on reactivity.

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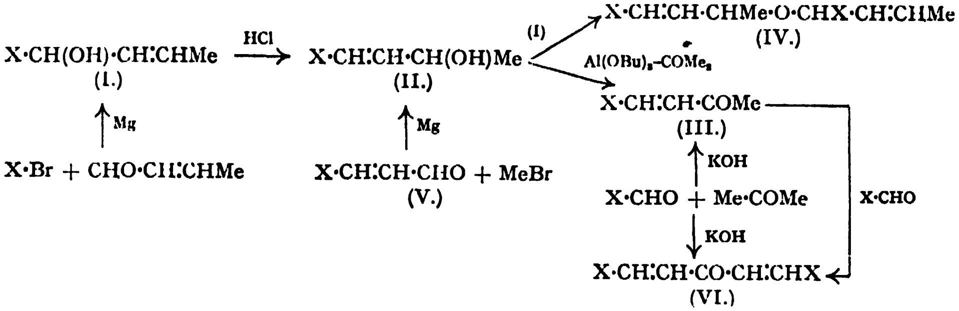
* A paper by Braude, Jones, and Stern, *J.*, 1947, 1087, is regarded as Part I.

The four *arylpropenylcarbinols* (*1-aryl-3-methylallyl alcohols*) (I), where X = 1-naphthyl, 2-naphthyl, 9-anthryl, and 9-phenanthryl, were prepared by the Grignard condensation of the appropriate aryl bromides with crotonaldehyde. After careful purification by fractionation in high vacuum or chromatography, the carbinols were obtained as low-melting crystalline solids, with the exception of the 1-naphthyl derivative which is a viscous liquid at room temperature.



On treatment with dilute hydrochloric acid in aqueous acetone at room temperature, the arylpropenylcarbinols were readily converted into the higher-melting *methyl-2-arylvinylcarbinols* (*3-aryl-1-methylallyl alcohols*) (II), which were also characterised by their p-*nitrobenzoates*. The isomerisations takes place practically quantitatively under suitable conditions and in sufficiently dilute solution. At high carbinol concentrations some self-etherification may occur; thus, a 7% solution of 1-naphthylpropenylcarbinol in 90% aqueous acetone–0·1M-hydrochloric acid afforded the rearranged carbinol in only 30% yield, together with a 55% yield of a higher-boiling product, which from its analytical data, its light absorption properties, and the absence of " active " hydrogen, must be formulated as the " half-rearranged " *ether* (IV) derived from one molecule of unrearranged, and one molecule of rearranged carbinol. On carrying out the rearrangement with a more dilute, 2·5%, solution of the carbinol in 60% aqueous acetone under otherwise identical conditions, the rearranged carbinol is obtained in 90% yield, and hardly any of the ether is formed. Self-etherification in the course of oxotropic rearrangement has previously been observed with ethynylpropenylcarbinol (I; X = CH⋮C) (Heilbron, Jones, and Weedon, *J.*, 1945, 81), but in this case the resulting ether was fully rearranged. These reactions are analogous to the easy cross-etherification of propenylcarbinols with methanol or ethanol which have also been shown to occur both with and without rearrangement in aqueous-alcoholic solution in the presence of dilute acids (Heilbron, Jones, and Weedon, *loc. cit.*; Braude, Jones, and Stern, *locc. cit.*; Braude and Stern, *loc. cit.*).

Although the 3-aryl-1-methylallyl alcohols (II) differ from the 1-aryl-3-methylallyl alcohols in their ultra-violet light-absorption properties, the spectral data do not in every case provide conclusive evidence for the structure of the rearranged carbinols (see below).. The structures of the latter were unambiguously proved, however, by Oppenauer oxidation to the methyl 2-arylvinyl ketones (III) which were obtained in good yields. The ketones were synthesised independently by condensation of the appropriate aryl aldehydes with acetone and characterised by their 2 : 4-*dinitrophenylhydrazones*. The preparation of methyl 2-1′- and methyl 2-2′-naphthylvinyl ketone has been previously described (Gibson, Hariharan, Menon, and Simonsen, *J.*, 1926, 2247; Wilds, Beck, Close, Djarassi, Johnson, Johnson, and Shunk, *J. Amer. Chem. Soc.*, 1947, 69, 1985). The reaction between 9-anthraldehyde and acetone in acid or alkaline solution was found to give largely the high-melting di-condensation product *di*-(*2-9′-anthrylvinyl*) *ketone* (VI; X = 9-anthryl) unless a large excess of acetone was employed. As might be expected in view of this result, the mono-condensation product, *methyl 2-9′-anthrylvinyl ketone* (III; X = 9-anthryl) condenses very readily with 9-anthraldehyde to give the di-condensation product. The condensation of 9-phenanthraldehyde with aqueous acetone in the presence of dilute sodium hydroxide also gave a mixture of products, which was separated by chromatography into (i) the desired *methyl 2-9′-phenanthrylvinyl ketone*, m. p. 85°, (ii) the hydroxy-ketone, 3-*keto*-1-9′-*phenanthrylbutan*-1-*ol*, m. p. 119°, and (iii) a high-melting *dimer* of methyl 2-9′-phenanthrylvinyl ketone, m. p. 274°, probably to be formulated as a *cyclo*butane derivative by analogy with similar dimers obtained from substituted styryl methyl ketones (Heilbron *et al.*, *J.*, 1927, 1888; 1928, 2323).

An alternative route to the 3-aryl-1-methylallyl alcohols is represented by the condensation of methylmagnesium bromide with the β-arylacraldehydes (V). The latter should be accessible *via* the arylaldehydes, but the reaction of acetaldehyde with both 1-naphthaldehyde and 9-anthraldehyde proved very sluggish. This is somewhat surprising in view of the high reactivity of the aryl aldehyde towards acetone (see above). In another attempt to prepare β-9′-anthrylacraldehyde (VI; X = 9-anthryl) *via* β-9′-anthrylacrylic acid, it was found that treatment of the acid with excess of thionyl chloride gave, not the required acid chloride, but a dichlorinated product which was readily hydrolysed to a monochloro-acid formulated as β-(10-*chloro*-9-*anthryl*)*acrylic acid*. This approach was not pursued.

The ultra-violet light-absorption data for the various derivatives are given in the table and n Figs. 1—4, and exhibit a number of interesting features. The absorptions of the 1-aryl-3-methylallyl alcohols (I) in this region are very similar to those of the unsubstituted polycyclic hydrocarbons, and practically identical with those of 1- and 2-methylnaphthalene, 9-methylanthracene and 9-methylphenanthrene severally, as far as these have been recorded (De Laszlo, *Z. physikal. Chem.*, 1925, **118**, 369; Jones, *Chem. Reviews*, 1947, **41**, 353; Askew, *J.*, 1935, 509). The spectral data thus provide very little evidence for any interaction between the aryl groups and the unconjugated ethylenic bond, such as observed (Braude, *J.*, 1949, 1902) in allylbenzene and certain related systems.

Ultra-violet light-absorption properties of 1-*aryl*-3-*methylallyl alcohols* (I), 3-*aryl*-1-*methylallyl alcohols* (II), *and methyl* 2-*arylvinyl ketones* (III) *in ethanol solution.*

(*c* = Concn. of absorbent in g.-mols./l. Cell thickness = 1 cm. throughout, except for X = Ph.)

		I.		II.		III.	
X.	*c*.	$\lambda_{max.}$, A.†	ε.	$\lambda_{max.}$, A.†	ε.	$\lambda_{max.}$, A.†	ε.
Phenyl [1,2]	—	2510	450	2480	19,000	2850	23,000
		2580	450	2510	19,500	—	—
		—	—	2810	2,000	—	—
		—	—	2910	1,550	—	—
1-Naphthyl	0·000021	2240	69,000 *	2280	51,000 *	2240	30,000
		2700	5,900	2960	10,000	2500	15,000
		2800	7,200	—	—	3300	11,500
		2900	5,200	—	—	—	—
	0·00021	3130	320	—	—	—	—
2-Naphthyl	0·000014	2260	95,000 *	*2390*	45,000 *	2370	16,500
		2740	6,300	2460	55,000 *	2450	16,500
		—	—	2540	50,000 *	*2650*	29,000
		—	—	*2750*	13,500	2720	32,000
		—	—	2840	16,500	3100	28,000
		—	—	2950	13,500	—	—
9-Anthryl	0·000012	2200	14,000	2200	10,500	2170	23,500
		2540	130,000 *	2550	115,000 *	2540	110,000
		3300	3,500	*3500*	6,000	3520	6,000
		3450	6,750	3600	8,500	3650	8,300
		3630	9,300	3820	8,000	3830	8,700
		3820	8,500	—	—	—	—
9-Phenanthryl	0·000021	*2440*	44,500	2400	34,500	2500	46,000
		2530	60,000	2570	48,000	3340	14,000
		2770	12,500	3010	13,500	—	—
		2950	11,000	*3050*	12,500		

* Strongly concentration-dependent.

† Figures in italics refer to inflections.

[1] Braude, Jones, and Stern, *J.*, 1946, 396.

[2] Lowry, Moureu, and MacConkey, *J.*, 1928, 3167.

With the 3-aryl-1-methylallyl alcohols (II), the bands are generally displaced towards longer wave-lengths, and the data for the naphthyl derivatives are very similar to those of 1-propenylnaphthalene (Pestemer and Manchen, *Monatsh.*, 1936, **68**, 92) and 2-vinylnaphthalene (Laitinen, Miller, and Parks, *J. Amer. Chem. Soc.*, 1947, **69**, 2707), respectively. The displacements are considerably smaller than those observed in comparing styrene with toluene, or cinnamyl alcohol with phenylvinylcarbinol. This is not unexpected since the additional conjugation due to the side-chain ethylenic group will be relatively smaller in the polycyclic systems. An exact comparison of the data for the unconjugated and conjugated derivatives is complicated by the vibrational structure of the bands, but for the purpose of discussion the highest of the vibrational peaks may be taken as the centre of the particular band system. The bands of all the polycyclic derivatives fall into two groups, a high-intensity system (subsequently denoted by "E") in the 2300—2600 A. region, and a low-intensity system (subsequently denoted by "B") in the 2900—3600 A. region. With the conjugated 1-naphthyl derivatives, the displacements of the E bands are smaller than those of the B bands, whereas the reverse applies in the case of the 2-naphthyl derivatives. Somewhat related observations

FIG. 1.

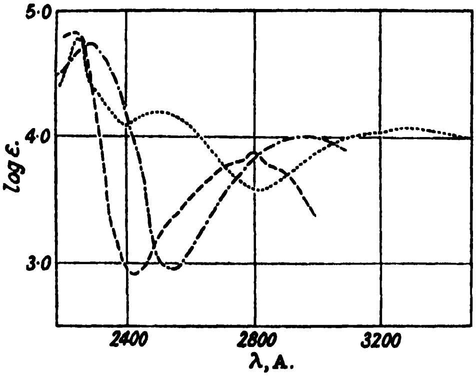


FIG. 2.

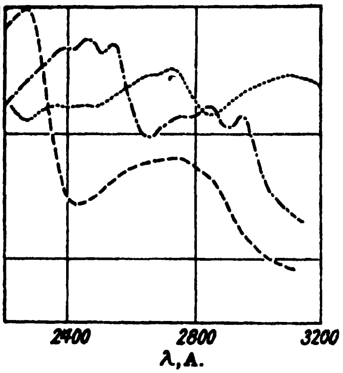
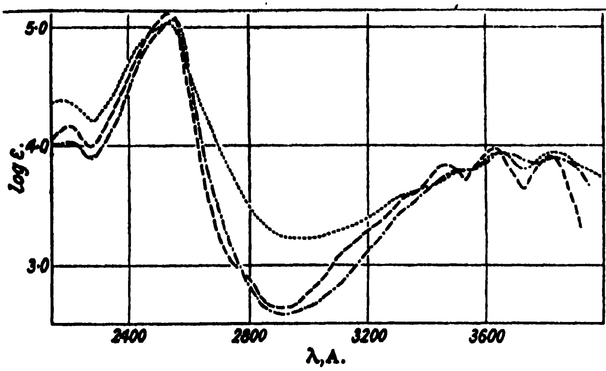


FIG. 1.—*Light absorption in ethanol of:* - - —— 1-(1-*Naphthyl*)-3-*methylallyl alcohol.*
—·—·— 3-(1-*Naphthyl*)-1-*methyllalyl alcohol.*
········ *Methyl* 2-1′-*naphthylvinyl ketone.*

FIG. 2.—*Light absorption in ethanol of:* ———— 1-(2-*Naphthyl*)-3-*methylallyl alcohol.*
—·—·— 3-(2-*Naphthyl*)-1-*methylallyl alcohol.*
- - - - *Methyl* 2-2′-*naphthylvinyl ketone.*

FIG. 3.

FIG. 4.



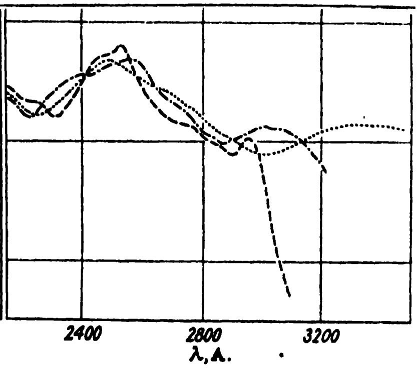


FIG. 3.—*Light absorption in ethanol of:* ———— 1-(9-*Anthryl*)-3-*methylallyl alcohol.*
—·—·— 3-(9-*Anthryl*)-1-*methylallyl alcohol.*
- - - - - - - *Methyl* 2-9′-*anthrylvinyl ketone.*

FIG. 4.—*Light absorption in ethanol of:* ———— 1-(9-*Phenanthryl*)-3-*methylallyl alcohol.*
—·—·— 3-(9-*Phenanthryl*)-1-*methylallyl alcohol.*
- - - - - - - *Methyl* 2-9′-*phenanthrylvinyl ketone.*

have been made by Jones (*loc. cit.*), who found that in anthracene derivatives, conjugating substituents in the 9-position produce smaller displacements of the E than of the B bands, whereas the reverse applies in the case of conjugating substituents in the 2-position. Jones put forward a tentative explanation of his observations in terms of the linear electronic oscillator model (Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273), assuming that the E and B bands arise from transitions polarised along the longer and shorter axis of the molecule, respectively. This assignment is in agreement with that deduced by Coulson (*Proc. Physical Soc.*, 1948, **60**, 257) from molecular-orbital calculations. The present observations on the spectral effects of an ethylenic substituent in the 1- and the 2-position of naphthalene may be explained in a similar way.* Another effect shown by the polycyclic derivatives in contrast to their phenyl analogues is that only the intensity of the B bands is increased, whilst that of the E bands is reduced, by the conjugated ethylenic group.

The absorption of 3-9′-phenanthryl-1-methylallyl alcohol exhibits bathochromic displacements similar to those of the 1-naphthyl derivative. 3-9′-Anthryl-1-methylallyl alcohol, on the other hand, differs from the other members of the series in that the wave-length locations of the maxima are practically identical with those of the unconjugated isomer, 1-9′-anthryl-3-methylallyl alcohol; moreover, the intensities of all the bands are considerably reduced as compared with the unconjugated isomer. A similar lack of spectral interaction has been observed by Jones (*loc. cit.*) in 9-phenylanthracene, and ascribed to the non-coplanarity of the phenyl and the anthryl groups owing to steric interference between the *o*-hydrogen atoms of the former and the 1- and 8-hydrogen atoms of the latter. Many other examples of the manifestation of steric inhibition of resonance in spectral properties have been described (for a summary and discussion, see Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890) and there can be little doubt that the anomalous absorption of 3-9′-anthryl-1-methylallyl alcohol also arises in this way. It will be observed that 3-9′-phenanthryl-1-methylallyl alcohol appears to exhibit normal absorption although free rotation should again be hindered; in this case, however, interference will only occur with the 8-hydrogen atom on one "side" of the molecule and a coplanar configuration is possible when the end of the side chain is inclined towards the 10-position.

The absorptions of the methyl 2-arylvinyl ketones (III) exhibit relationships similar to those shown by the 3-aryl-1-methylallyl alcohols and need not be discussed in detail. As would be expected, the bathochromic displacements are somewhat greater with the ketones than with the alcohols, but very much smaller than those shown by the phenyl analogue, styryl methyl ketone. The absorption of the 9-anthryl derivative again shows an almost complete lack of bathochromic displacements, probably owing to steric hindrance. The same effect is observed in the structurally related *oo*′-dimethylstyryl methyl ketone (Braude, Jones, and Sondheimer, forthcoming publication).

Another interesting feature associated with the spectra of the polycyclic derivatives is that the intensity of some of the bands appears to be strongly concentration-dependent (see Table I). This phenomenon is also shown in varying degrees by the parent hydrocarbons and is due to the superposition of absorption and fluorescence-emission (Braude, Fawcett, and Timmons, *J.*, in the press). The fluorescence activity of the different bands varies greatly; it is particularly marked in the high-intensity (E) bands of the anthryl derivatives and naphthylcarbinols, but almost absent in the phenanthryl derivatives and the methyl 2-naphthylvinyl ketones. Solutions of 3-9′-anthryl-1-methylallyl alcohol exhibit strong visible fluorescence in daylight.

EXPERIMENTAL.

(Light-absorption data are only given when not included in Table I.)

1-1′-*Naphthyl*-3-*methylallyl Alcohol* (I; X = 1-Naphthyl).—Freshly distilled crotonaldehyde (35 g.) in ether (100 ml.) was added to 1-naphthylmagnesium bromide (from magnesium, 12 g., and 1-bromonaphthalene, 104 g.) in ether (500 ml.) during 2 hours at 0° in an atmosphere of nitrogen. Stirring was continued for 2 hours and excess of saturated ammonium chloride solution was then added during ½ hour at 0°. The ethereal layer was separated, dried (Na_2SO_4), and distilled in a high vacuum from a trace of anhydrous potassium carbonate. A small amount of naphthalene (*ca.* 0·5 g.) sublimed first and then 1-1′-*naphthyl*-3-*methylallyl alcohol* (61 g., 62%) distilled as viscous oil, b. p. 110° (bath)/10^{-5} mm., n_D^{19} 1·6218 (Found: C, 85·0; H, 7·1. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). Shurakowski (*J. Phys. Chem. Russia*, 1909, **41**, 1687) gives b. p. 204—206°/22 mm. The p-*nitrobenzoate* separated from light petroleum (b. p. 60—80°) in colourless crystals, m. p. 118—119° (Found: N, 4·1. $C_{21}H_{17}O_4N$ requires N, 4·0%). Light absorption in ethanol: Maxima, 2230 and 2640 A., ε = 87,000 and 19,000, respectively. On prolonged storage in contact with air, the carbinol is slowly converted into the conjugated isomer (below), as a result of the formation of small amounts of acidic oxidation products.

3-1′-*Naphthyl*-1-*methylallyl Alcohol* (II; X = 1-Naphthyl).—(*a*) 1-1′-Naphthyl-3-methylallyl alcohol (5 g.) was dissolved in 60% aqueous acetone–0·1M-hydrochloric acid (200 ml.), and the solution kept for 24 hours at room temperature. On dilution with water 3-1′-*naphthyl*-1-*methylallyl alcohol* (4·5 g.) separated as an oil, which was distilled at 95° (bath)/10^{-5} mm. It solidified on storage at 0° and crystallised from pentane in colourless plates, m. p. 41—42° (Found: C, 85·1; H, 7·3. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). The p-*nitrobenzoate* crystallised from light petroleum (b. p. 60—80°) in very pale yellow needles, m. p. 93° (Found: C, 73·0; H, 5·0; N, 4·1. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 4·9; N, 4·0%). Light absorption in ethanol: Maxima, 2280, 2600, and 2910 A., ε = 61,000, 17,500, and 14,000, respectively.

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* Since this paper was written, a longitudinal polarisation of the 2300 A. band and a transverse polarisation of the 2900 A. band of naphthalene have also been deduced by Klevens and Platt (*J. Chem. Physics*, 1949, **17**, 470).

(*b*) 1-1′-Naphthyl-3-methylallyl alcohol (5 g.) was dissolved in 90% aqueous acetone–0·1M-hydrochloric acid (75 ml.), and the solution kept for 24 hours at room temperature. On dilution with water an oil separated, which was distilled at 10^{-5} mm., giving 3-1′-naphthyl-1-methylallyl alcohol, b. p. 95° (bath) (1·5 g., 30%), and a high-boiling fraction, b. p. 250° (bath) (2·75 g., 55%). On cooling, the high-boiling fraction set to a glassy solid which failed to react with sodium or methylmagnesium iodide in ether. On the basis of this evidence and the analytical and light-absorption data it is formulated as 1-1′-*naphthyl*-3-*methylallyl* 3-1′-*naphthyl*-1-*methylallyl ether* (Found: C, 88·4; H, 6·9. $C_{28}H_{26}O$ requires C, 88·8; H, 6·9%). Light absorption in ethanol: Maxima, 2260 and 2820 A., ε = 130,000 and 17,000, respectively.

Methyl 2-1′-*Naphthylvinyl Ketone* (III; X = 1-Naphthyl).—(*a*) 1-Naphthaldehyde (4 g.; Hinkel, Ayling, and Beynon, *J.*, 1936, **342**), acetone (30 ml.), and 1% sodium hydroxide (100 ml.) were stirred together at 40° for 24 hours. Ether extraction and distillation yielded the ketone (4 g., 80%), b. p. 142°/5 × 10^{-4} mm., n_D^{20} 1·6670 (Wilds *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 1985, give b. p. 163—173°/0·9 mm., n_D^{25} 1·6665). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 261° (Found: C, 64·0; H, 4·4; N, 15·0. $C_{20}H_{16}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%). Light absorption in chloroform: Maxima, 2560, 3230, and 3970 A., ε = 32,500, 16,000, and 37,500, respectively.

(*b*) 3-1′-Naphthyl-1-methylallyl alcohol (2 g.), aluminium *tert.*-butoxide (2·5 g.), dry acetone (20 ml.), and benzene (20 ml.) were refluxed together for 24 hours. Decomposition with excess of sulphuric acid, ether-extraction, and distillation yielded 1-naphthylmethyleneacetone, b. p. 85°/10^{-5} mm., n_D^{22} 1·6580 (1·3 g., 65%), which gave a 2 : 4-dinitrophenylhydrazone, m. p. 261°, undepressed on admixture with the authentic specimen.

1-2′-*Naphthyl*-3-*methylallyl Alcohol* (I; X = 2-Naphthyl).—2-Bromonaphthalene (52 g., Newman and Wise, *J. Amer. Chem. Soc.*, 1941, **63**, 2847) in ether (200 ml.) was added slowly to a suspension of magnesium (6 g.) in ether (200 ml.) containing ethyl bromide (0·5 g.), and the mixture was stirred for 2 hours in an atmosphere of nitrogen. Freshly distilled crotonaldehyde (18 g.) in ether (30 ml.) was then added slowly at 0°, and stirring continued for a further 3 hours. Decomposition of the Grignard complex with ammonium chloride solution, isolation of the product in the usual manner, and distillation from a trace of anhydrous potassium carbonate afforded 2 : 2′-dinaphthyl, m. p. 175° (0·5 g.), and 1-2′-*naphthyl*-3-*methylallyl alcohol* (27 g., 55%), b. p. 90° (bath)/10^{-5} mm., n_D^{22} 1·6190, which solidified when kept and crystallised from pentane in fine needles, m. p. 43—44° (Found: C, 84·8; N, 7·1. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%).

3-2′-*Naphthyl*-1-*methylallyl Alcohol* (II; X = 2-Naphthyl).—1-2′-Naphthyl-3-methylallyl alcohol (5 g.) was dissolved in 60% aqueous acetone–0·1M-hydrochloric acid (200 ml.), and the solution kept for 24 hours at room temperature. On dilution with water, 3-2′-*naphthyl*-1-*methylallyl alcohol* (4·8 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in fine needles, m. p. 94° (Found: C, 85·1; H, 7·1. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). The p-*nitrobenzoate* separated from light petroleum (b. p. 80—100°) in crystals, m. p. 113° (Found: C, 72·7; H, 5·1; N, 4·0. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 4·9; N, 4·0%). Light absorption in chloroform: Maxima, 2510, 2570, 2700, 2780, 2890, 2990, and 3410 A., ε = 55,500, 28,000, 21,500, 19,000, 15,500, and 1,100, respectively.

Methyl 2-2′-*Naphthylvinyl Ketone* (III; X = 2-Naphthyl).—3-2′-Naphthyl-1-methylallyl alcohol (2·5 g.), aluminium *tert.*-butoxide (3 g.), dry acetone (30 ml.), and benzene (30 ml.) were refluxed together for 24 hours. Decomposition with sulphuric acid gave the ketone (1·5 g.), which separated from methanol as crystals, m. p. 103—104° (Wilds *et al.*, *loc. cit.*, give m. p. 104°). The 2 : 4-*di-nitrophenylhydrazone* crystallised from pyridine in needles, m. p. 268° (Found: C, 64·1; H, 4·5; N, 14·9. $C_{20}H_{16}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%). Light absorption in chloroform: Maxima, 3160 and 3980 A., ε = 19,000 and 37,500, respectively.

1-9′-*Anthryl*-3-*methylallyl Alcohol* (I; X = 9-Anthryl).—9-Bromoanthracene (26 g., Barnett and Cook, *J.*, 1924, **125**, 1084) in ether (200 ml.) was refluxed with ethyl bromide (11 g.) and magnesium (4·9 g.) for 24 hours. Freshly distilled crotonaldehyde (14 g.) in ether (50 ml.) was then added slowly to the ice-cold suspension, and stirring continued for 1 hour. Decomposition of the Grignard complex with ammonium chloride, and isolation of the product afforded 1-9′-*anthryl*-3-*methylallyl alcohol* (17 g., 68%), which crystallised from hot ethyl acetate–light petroleum (b. p. 40—60°) in very pale yellow crystals, m. p. 114° (Found: C, 87·0; H, 6·4. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

3-9′-*Anthryl*-1-*methylallyl Alcohol* (II; X = 9-Anthryl).—1-9′-Anthryl-3-methylallyl alcohol (5 g.) was dissolved in 60% aqueous acetone–0·1M-hydrochloric acid, and the solution kept for 24 hours at room temperature. On dilution with water, 3-9′-*anthryl*-1-*methylallyl alcohol* (4·9 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in yellow needles, m. p. 116° (Found: C, 86·9; H, 6·65. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%). The p-*nitrobenzoate* crystallised from light petroleum (b. p. 80—100°) in orange needles, m. p. 150° (Found: C, 75·6; H, 5·0; N, 3·6. $C_{25}H_{19}O_4N$ requires C, 75·6; H, 4·8; N, 3·5%). Light absorption in ethanol: Maxima, 2560, 3510, 3670, and 3860 A., ε = 155,000, 6,500, 8,500, and 7,100, respectively.

Methyl 2-9′-*Anthrylvinyl Ketone* (III; X = 9-Anthryl).—(*a*) A mixture of 9-anthraldehyde (2 g.; Fieser, Hartwell, and Jones, *Org. Synth.*, **20**, 11), acetone (20 ml.), and 10% sodium hydroxide (1 ml.) was kept at room temperature for 24 hours. Filtration yielded 1 : 5-*di*-9′-*anthrylpenta*-1 : 4-*dien*-3-*one* (0·4 g., 18%), which crystallised from pyridine in orange plates, m. p. 293° (Found: C, 91·2; H, 4·9. $C_{33}H_{22}O$ requires C, 91·2; H, 5·1%). Light absorption in chloroform: Maxima, 2520, 2560, and 3850 A., ε = 14,500, 14,500, and 13,500, respectively. Addition of water to the filtrate gave *methyl* 2-9′-*anthrylvinyl ketone* (1·4 g., 56%), which crystallised from ethanol in yellow needles, m. p. 113° (Found: C, 88·0; H, 5·8. $C_{18}H_{14}O$ requires C, 87·8; H, 5·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 244° (Found: C, 67·5; H, 4·2; N, 13·1. $C_{24}H_{18}O_4N_4$ requires C, 67·6; H, 4·3; N, 13·1%). Light absorption in chloroform: Maxima, 4080 A., ε = 22,500. On one occasion, a different di-condensation product, probably a stereoisomeric 1 : 5-*di*-9′-*anthrylpenta*-1 : 4-*dien*-3-*one*, m. p. 268°, was obtained (Found: C, 91·4; H, 5·4. $C_{33}H_{22}O$ requires C, 91·2; H, 5·1%). Light absorption in chloroform: Maxima 2510, 2560, and 3680 A., ε = 110,000, 105,000, and 7,200 respectively.

(*b*) 3-9′-Anthryl-1-methylallyl alcohol (0·8 g.), aluminium *tert.*-butoxide (2 g.), dry acetone (10 ml.), and benzene (10 ml.) were refluxed together for 24 hours. Decomposition with sulphuric acid and ether extraction gave a viscous oil, which crystallised from ethanol to give methyl 2-9′-anthrylvinyl ketone, m. p. 112°, undepressed on admixture with the authentic specimen.

1 : 5-*Di*-9′-*anthrylpenta*-1 : 4-*dien*-3-*one*.—A solution of 9-anthrylmethyleneacetone (0·5 g.) and 9-anthraldehyde (0·5 g.) in dry ethyl acetate (10 ml.) was saturated with dry hydrogen chloride and kept for 2 hours. The 1 : 5-di-9′-anthrylpenta-1 : 4-dien-3-one (0·8 g.) was filtered off, and crystallised from pyridine in orange plates, m. p. 291°, undepressed on admixture with the specimen obtained above.

1-9′-*Phenanthryl*-3-*methylallyl alcohol* (I; X = 9-Phenanthryl).—9-Bromophenanthrene (21 g.; Austin, *J.*, 1908, **93**, 1763) and ethyl bromide (9 g.) in a mixture of benzene (100 ml.) and ether (100 ml.) were added slowly to a suspension of magnesium (4 g.) in ether (100 ml.), stirred for 1 hour and then refluxed for 7 hours. Freshly distilled crotonaldehyde (11·5 g.) in ether (50 ml.) was added slowly at 0°, and stirring continued for 2 hours. Decomposition of the Grignard complex with ammonium chloride, isolation of the product, and vacuum distillation gave an oil which did not solidify. This was chromatographed from benzene solution on an alumina column, a mixture of benzene and ethanol being used as eluent, to give solid 1-9′-*phenanthryl*-3-*methylallyl alcohol* (15 g., 75%), which crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 88—89° (Found: C, 86·8; H, 6·4. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

3-9′-*Phenanthryl*-1-*methylallyl Alcohol* (II; X = 9-Phenanthryl).—1-9′-Phenanthryl-3-methylallyl alcohol (3 g.) was dissolved in 60% aqueous acetone–0·1M-hydrochloric acid (200 ml.), and the solution set aside for 24 hours at room temperature. On dilution with water 3-9′-*phenanthryl*-1-*methylallyl alcohol* (2·7 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 103° (Found: C, 87·3; H, 6·6. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%). The p-*nitrobenzoate* crystallised from *cyclo*hexane in colourless needles, m. p. 122° (Found: C, 75·9; H, 4·8; N, 3·7. $C_{25}H_{19}O_4N$ requires C, 75·6; H, 4·8; N, 3·5%). Light absorption in ethanol: Maxima, 2550 and 3050 A., ε = 53,500 and 15,000, respectively.

Methyl 2-9′-*Phenanthrylvinyl Ketone* (III; X = 9-Phenanthryl).—3-9′-Phenanthryl-1-methylallyl alcohol (1 g.) and aluminium *tert.*-butoxide (2 g.) in dry acetone (10 ml.) and benzene (10 ml.) were refluxed for 24 hours. Decomposition with sulphuric acid and ether extraction gave a viscous oil, which crystallised from ethanol to give the ketone (0·6 g., 60%). The 2 : 4-dinitrophenylhydrazone crystallised from pyridine in needles, m. p. 268°, undepressed on admixture with the authentic specimen obtained below.

Reaction between 9-*Phenanthraldehyde and Acetone*.—A mixture of 9-phenanthraldehyde (3 g.; Miller and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 766), acetone (40 ml.), and 10% sodium hydroxide (1 ml.) was kept at room temperature for 24 hours. Addition of water to the mixture gave a viscous gum which did not solidify. This was chromatographed from benzene solution on an alumina column to give 3 products as follows.

(i) *Methyl* 2-9′-*phenanthrylvinyl ketone* (1·5 g., 40%), which crystallised from aqueous acetone in pale yellow crystals, m. p. 85° (Found: C, 87·5; H, 5·8%; *M*, in camphor, 251. $C_{18}H_{14}O$ requires C, 87·8; H, 5·7%; *M*, 246). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in needles, m. p. 269° (Found: C, 67·7; H, 4·4; N, 12·9. $C_{24}H_{18}O_4N_4$ requires C, 67·6; H, 4·3; N, 13·1%). Light absorption in chloroform: Maxima, 2560, 3240, and 2980 A., ε = 57,000, 14,500, and 36,000, respectively.

(ii) 3-*Keto*-1-9′-*phenanthrylbutan*-1-*ol* (0·96 g., 25%), which crystallised from light petroleum (b. p. 80—100°) in colourless needles, m. p. 119° (Found: C, 82·1; H, 6·3. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). Light absorption in ethanol: Maxima, 2530, 2970, 3250, 3320, 3410, and 3480 A., ε = 71,000, 13,000, 290, 330, 260, and 290, respectively. The 2 : 4-*dinitrophenylhydrazone* separated from aqueous pyridine in orange crystals, m. p. 256° (Found: C, 65·0; H, 4·7; N, 12·8. $C_{24}H_{20}O_5N_4$ requires C, 64·9; H, 4·5; N, 12·6%). Light absorption in chloroform: Maxima, 2560, 2900, 2990, and 3600 A., ε = 67,000, 13,500, 14,500, and 22,000, respectively.

(iii) A *dimer* of methyl 2-9′-phenanthrylvinyl ketone (0·4 g., 10%), which separated from pyridine as colourless plates, m. p. 274° (Found: C, 87·7; H, 6·0; *M*, in camphor, 450. $C_{36}H_{28}O_2$ requires C, 87·8; H, 5·7%; *M*, 492). Light absorption in chloroform: Maxima, 2560, 2800, 2910, and 3010 A., ε = 125,000, 27,000, 23,000, and 28,000, respectively.

Reaction between Anthrylacrylic Acid and Thionyl Chloride.—Anthrylacrylic acid (2 g.; Davis and Carmack, *J. Org. Chem.*, 1947, **12**, 76) was refluxed with thionyl chloride (1·7 g.) for 30 minutes. The product solidified on cooling and crystallised from benzene in yellow-brown needles, m. p. 204° (1·8 g., 75%), and is formulated as β-(9-*chloro*-10-*anthryl*)*acryloyl chloride* (Found: C, 67·4; H, 3·5. $C_{17}H_{10}OCl_2$ requires C, 67·8; H, 3·3%). The acid chloride (1·8 g.) was refluxed with 10% potassium hydroxide (20 ml.) for 30 minutes. The reaction mixture was acidified, and crystallisation of the product from nitrobenzene gave a chloro-acid, m. p. 264° (1·6 g., 95%), formulated as β-(9-*chloro*-10-*anthryl*)*acrylic acid* (Found: C, 72·1; H, 4·2. $C_{17}H_{11}O_2Cl$ requires C, 72·2; H, 3·9%). Light absorption in ethanol: Maxima, 2580, 3770, and 3970 A., ε = 155,000, 9,600, and 9,400, respectively.

Reaction between 1-*Naphthaldehyde and Acetaldehyde*.—Acetaldehyde (2 g.) was slowly added to a stirred solution of 1-naphthaldehyde (2 g.) and 10% sodium hydroxide (2 ml.) in aqueous methanol (20 ml.). Ether extraction of the reaction mixture gave an oil, which on distillation gave unchanged 1-naphthaldehyde (0·5 g.) and a high-boiling fraction which did not solidify. Similar results were obtained when using piperidinium acetate as a catalyst.

Reaction between 9-*Anthraldehyde and Acetaldehyde*.—Acetaldehyde (2 g.) was caused to react with 9-anthraldehyde (2 g.) under similar conditions to the above. Ether extraction gave a gum which could not be solidified.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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159. *The Kinetics of Anionotropic Rearrangement. Part IX. The Effects of Polycyclic Aromatic Substituents on Reactivity. A Comparison of the Electronic Properties of the Phenyl, 1-Naphthyl, 2-Naphthyl, 9-Anthryl, and 9-Phenanthryl Groups.*

By E. A. Braude and J. S. Fawcett.

The kinetics of the acid-catalysed oxotropic rearrangements of a number of polycyclic 1-aryl-3-methylallyl alcohols (I) to the corresponding 3-aryl-1-methylallyl alcohols (II) have been determined in aqueous dioxan solution. The results are compared with those previously obtained for the rearrangement of 1-phenyl-3-methylallyl alcohol (phenylpropenylcarbinol) (I; X = Ph) and appear to provide the first comprehensive set of quantitative kinetic data on a series of polycyclic aromatic derivatives. The rate constants at one temperature increase in the sequence 9-phenanthryl < phenyl < 2-naphthyl ~ 1-naphthyl < 9-anthryl, but the differences are relatively small and there is little variation in either the energies of activation or the probability factors.

The results are discussed in relation to existing evidence concerning the reactivity of polycyclic aromatic systems. Qualitatively, they are in agreement with the predictions of both valency-bond resonance and molecular-orbital theory, except for the phenanthryl derivative. An explanation for this anomaly is suggested. Quantitatively, the results for the naphthyl and anthryl derivatives show a closer correlation with simple valency-bond resonance theory than with molecular-orbital calculations, and a linear relation is found to hold between the rate constants at one temperature and the expected number of contributing polar resonance forms.

In earlier work in this series (Part V, *J.*, 1946, 396; Part VI, *J.*, 1947, 1096; Part VIII, *J.*, 1948, 1982), the rearrangement of 1-phenyl-3-methylallyl alcohol (phenylpropenylcarbinol) (I; X = Ph) to 3-phenyl-1-methylallyl alcohol (styrylmethylcarbinol) (II; X = Ph) has been investigated in some detail. The isomerisation proceeds with great facility and without side reactions in dilute acid solution, and its mechanism under these conditions can now be regarded as established with a reasonable degree of certainty. It has also been shown that this type of rearrangement is very sensitive to structural changes, being facilitated by electron-donating and hindered by electron-attracting substituents, as required by its mechanism. Since a wide variety of analogues of 1-phenyl-3-methylallyl alcohol is fairly readily accessible synthetically, this affords an excellent basis for investigating the electronic properties of substituents which have not yet been studied in this respect because of a lack of suitable reactions or for other reasons. This applies to a surprisingly large number of common and important groups. Polycyclic and heterocyclic organic chemistry, in particular, are almost devoid of quantitative reactivity data, and theoretical work has considerably outstripped experimental advances in this field.

$$\text{(I.)}\quad X{\cdot}CH(OH){\cdot}CH{:}CHMe \longrightarrow X{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}Me \quad \text{(II.)}$$

The present communication deals with a kinetic study of the rearrangements of some polycyclic 1-aryl-3-methylallyl alcohols (I; X = 1-naphthyl, 2-naphthyl, 9-anthryl, and 9-phenanthryl), the synthesis and rearrangements of which have been described (Braude, Fawcett, and Newman, preceding paper). The rate constants, energies of activation, and probability factors under standard conditions employed in earlier studies are collected in Tables I and II. As before, the reaction rates were determined spectrometrically, advantage being taken of the differences between the ultra-violet light absorption of 1-aryl-3-methylallyl and the isomeric 3-aryl-1-methylallyl alcohols. A complication arose with the 9-anthryl derivative owing to the intense fluorescence of the rearranged carbinol, but this could be overcome by suitable choice of wave-lengths (see Experimental). Good first-order rate constants were obtained throughout, and the final absorption intensities at the wave-lengths chosen were identical within experimental error with those of the pure 3-aryl-1-methylallyl alcohols, showing that no measurable equilibria were set up. The usual solvent effects were observed, the rate constants being decreased about threefold, and the Arrhenius energies of activation increased by about 3 kcals./mol., in 80% as compared with 60% aqueous dioxan. The rate constants at one temperature increase in the sequence 9-phenanthryl < phenyl < 2-naphthyl ≈ 1-naphthyl < 9-anthryl, but the differences are small and only cover a range of fivefold variation. The values for the two naphthyl derivatives lie especially close together and their order depends on the temperature, the rearrangement of the 1-naphthyl derivative being a little faster below 50°, and a little slower above 50°, than that of the 2-naphthyl derivative. The Arrhenius energies of activation and probability factors for a particular medium are practically constant throughout the series; the differences in energy of activation only slightly exceed the uncertainty in the Arrhenius plots (*ca.* ±0·3 kcal./mol.).

The rearrangement of the lower homologues, 1-naphthyl- and 2-naphthyl-vinylcarbinol, has been examined qualitatively by Burton (*J.*, 1931, 759), who concluded from indirect evidence (the degree of rearrangement accompanying *p*-nitrobenzoylation) that the ease of isomerisation increases in the order phenyl < 2-naphthyl < 1-naphthyl.

TABLE I.

First-order rate constant (10^4 k, *min*$^{-1}$.) *for the rearrangements of* 1-*aryl*-3-*methylallyl alcohols* (I) *to* 3-*aryl*-1-*methylallyl alcohols* (II) *in aqueous dioxan*–0·01M-*hydrochloric acid.*

[Concentration of alcohols, 0·001—0·01M.; c_S = dioxan concentration (% v/v).]

Temp.	c_s.[*]	X = Phenyl.[1]	2-Naphthyl.	1-Naphthyl.	9-Anthyrl.	9-Phenanthryl.
0°	60	5·4	8·0	8·3	25	4·0
30	60	184	320	345	805	146
	80	69	126	129	315	66
40	60	545	800	840	2,050	445
	80	—	400	405	1,050	210
50	60	1510	2450	2450	6,500	1280
	80	—	1300	1180	3,200	700
60	60	3650	6100	5300	14,500	3200
	80	—	3300	2900	6,650	1890

[*] Values for c_s = 80% at 0° are omitted, as solid dioxan tended to crystallise in the media.

[1] Braude, Jones, and Stern, *J.*, 1946, 396. The value for c_s = 80% at 30° is extrapolated from measurements at higher acid concentrations.

TABLE II.

Relative rate constants (r), *Arrhenius energies of activation, and probability factors.*

($k/c_A = Ae^{-E_{Arr.}/RT}$, where c_A = acid concentration.)

	60% Aqueous dioxan.			80% Aqueous dioxan.		
X.	*r*.[*]	$E_{Arr.}$.	log *A*.	*r*.[*]	$E_{Arr.}$.	log *A*.
Phenyl [1]	1	19·5	12·6	1	—	—
2-Naphthyl	1·74	20·2	13·3	1·82	22·4	14·5
1-Naphthyl	1·88	19·9	13·1	1·87	22·0	14·2
9-Anthryl	4·37	19·5	13·2	6·32	22·0	14·6
9-Phenanthryl	0·80	20·3	13·1	0·96	22·6	14·4
(Vinyl [2])	0·78	—	—	0·67	—	—

[*] At 30°.

[1] Braude, Jones, and Stern, *loc. cit.*

[2] Braude and Jones, *J.*, 1946, 128. (Extrapolated from measurements in aqueous ethanol.)

DISCUSSION.

(1) *Correlation of Available Data on the Reactivity of Polycyclic Aromatic Compounds.*—The reactivity of the polycyclic aromatic hydrocarbons is generally stated to increase in the order benzene < naphthalene < phenanthrene < anthracene. This sequence is based on a wealth of *qualitative* data concerning, particularly, the ease of sulphonation, nitration, bromination, hydrogenation, and oxidation, and although it is a commonplace that such qualitative comparisons of reactivity without kinetic control can be misleading, there is no reason to doubt the validity of the general result in the present case. The reactions enumerated above include both heterolytic and homolytic types, and it is of some interest that the different types of reactivity appear to run parallel in this series; however, we are here concerned only with heterolytic reactivity and therefore confine attention to sulphonation and nitration which almost certainly involve attack by the entities SO_3H^+ and NO_2^+ under the usual conditions (for references, see Braude, *Ann. Reports*, 1949, **46**, in the press). The results for naphthalene are clear-cut, both sulphonation and nitration proceeding with comparable speed at lower temperatures than those required for benzene, and substitution in the 1- being somewhat faster than in the 2-position. Phenanthrene is sulphonated and nitrated with comparable speed at a lower temperature than naphthalene, but the evidence concerning the reactivity of the different positions is somewhat conflicting; it appears that the 9-, 2-, and 3-positions are most readily substituted, with the reactivity probably decreasing in that order (cf. Fieser, *J. Amer. Chem. Soc.*, 1929, **51**, 2460). Finally, anthracene undergoes electrophilic substitution somewhat more readily still, but here sulphonation is faster in the 1- and 2-positions, whereas nitration is fastest in the 9-position. The abnormal orientation of the sulphonation of anthracene is probably due

to steric hindrance which will first become effective at the " flanked " *meso*-positions and with large reagents, such as SO_3H^+.

Some kinetic measurements on the halogenation of polycyclic aromatic hydrocarbons have been recorded (Lauer and Oda, *Ber.*, 1936, **69**, 141, 146, 851; Robertson, De La Mare, and Johnston, *J.*, 1943, 276; De la Mare and Robertson, *ibid.*, p. 279; Wibaut and Sixma, *Proc. K. Akad. Wetensch. Amsterdam*, 1948, **51**, 776), but they do not readily lend themselves to comparison owing to the different conditions employed and owing to the incursion of catalytic effects; the brominations of anthracene and phenanthrene are further complicated by the simultaneous occurrence of substitution and addition reactions (Price, *J. Amer. Chem. Soc.*, 1936, **58**, 1834, 2101; Fieser and Price, *ibid.*, p. 1838).

Most of the scant *quantitative* data to be found in the literature regarding the reactivity of polycyclic aromatic compounds, as well as the present results, concern side-chain reactions (see Table III). Shoesmith and Rubli (*J.*, 1927, 3098) and Ingold and Patel (*J. Indian. Chem. Soc.*, 1930, **7**, 95) investigated the neutral hydrolysis and alcoholysis of benzyl, 2-naphthylmethyl, and 1-naphthylmethyl bromides in 90% aqueous alcohol and obtained rate constants increasing in that order. Bergmann and Hirshberg (*J.*, 1936, 331) determined the rates of alkaline hydrolysis of methyl 1- and methyl 2-naphthoate in aqueous methanol of unstated composition and found that the 1- reacted slightly faster than the 2-naphthyl ester. The rate constants for both naphthyl derivatives are smaller than a quoted value for methyl benzoate, but this comparison may not be significant since the solvent conditions are not necessarily identical. Recently, Gordon, Miller, and Day (*J. Amer. Chem. Soc.*, 1948, **70**, 1946; 1949, **71**, 1245) have measured the rates of ammonolysis of alkyl and aryl acetates in anhydrous ethylene glycol and found that the naphthyl esters react about 100 times more *slowly* than phenyl acetate. The effective reagent in this reaction is believed to be a relatively large ammonia–glycol complex, and the exceptionally low reactivity of the polycyclic derivatives is ascribed to steric hindrance. The only previous kinetic data for polycyclic systems other than naphthyl derivatives appear to come from Shoppee's study (*J.*, 1933, 40) of the reversible prototropic rearrangements of 1-phenyl-3-arylmethyleneazomethines. The order of mobilities was found to be 9-phenanthryl < 2-naphthyl < 1-naphthyl, but no value could be obtained for the phenyl substituent since the 1 : 3-diphenyl derivative is completely symmetrical.

TABLE III.

Relative reactivities (reaction rates) of polycyclic aromatic derivatives.

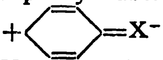
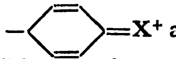
X.	(1).	(2).	(3).	(4).	(5).	(6).
Phenyl	[1]	1	—	1	—	1
2-Naphthyl	[2]	1·74	0·88	1·68	0·83	0·01
1-Naphthyl	[3]	1·88	1	2·16	1	0·01
9-Anthryl	[5]	4·37	—	—	—	—
9-Phenanthryl	[4]	0·80	0·65	—	—	—
(Vinyl)	—	0·78	—	—	—	0·24

(1) Sequence of ease of nitration of hydrocarbons derived from qualitative data. (2) Oxotropic rearrangement of 1-aryl-3-methylallyl alcohols at 30° (this paper). (3) Prototropic rearrangement of 1-phenyl-3-arylmethyleneazomethines at 86° (Shoppee, *loc. cit.*). (4) Neutral hydrolysis of arylmethyl bromides at 25° (Shoesmith and Rubli, *loc. cit.*). (5) Alkaline hydrolysis of methyl naphthoates at 60° (Bergmann and Hirshberg, *loc. cit.*). (6) Ammonolysis of aryl acetates at 30° (Gordon, Miller, and Day, *loc. cit.*).

Summarising the available evidence, and neglecting exceptions probably conditioned by steric hindrance, we find the same order of increasing heterolytic reactivity, phenyl < 2-naphthyl < 1-naphthyl < 9-anthryl, to apply to both nuclear and side-chain reactions. The position of the 9-phenanthryl group, on the other hand, varies; it is below 9-anthryl in nuclear cationoid substitution, below naphthyl (and possibly phenyl) in side-chain prototropy, and below phenyl in side-chain oxotropy.

(2) *Qualitative Theory.*—The generally accepted basis of the electronic theory of substituent effects is that substituents increase or decrease, as the case may be, the electron-availability at the point of reaction and thereby increase or decrease the energy of activation (E) of the heterolytic fission, depending on the electronic requirements of the latter (cf. Hinshelwood, Laidler, and Timm, *J.*, 1938, 848). Steric and related factors, on the other hand, are known to influence both the energy of activation and the probability factor (A) or entropy of activation. The only comparable kinetic measurements on a series of polycyclic aromatic compounds which allow analysis of differences in activation energies and probability factors appear to be those reported in the present work. The total variation in rate constants is too small, however, to

provide a clear distinction as to the extent to which differences in *E* or *A* (both of which are almost within experimental uncertainty) contribute to variations in *k*. Nevertheless, since earlier work on the effects of benzenoid and other substituents (cf. Part VI, *J.*, 1947, 1096) and unpublished work on the effects of heterocyclic substituents has shown that differences in *k* were mainly due to differences in *E*, it will be assumed that the same applies in the polycyclic series. This assumption is supported by the work of Wibaut and Sixma (*loc. cit.*), according to which the differences in the rates of bromination of naphthalene in the 1- and the 2-position are almost entirely due to differences in *E*. It therefore appears justified, in the subsequent discussion, to employ differences in reaction rates directly as a measure of the electronic effects of substituents.

As previously (cf. Part VI, *loc. cit.*), we adopt Ingold's convention (*Chem. Reviews*, 1934, **15**, 233) of inductive (*I*) and tautomeric (*T*) effects, negative signs referring to electron-attraction and positive signs to electron-donation. The tautomeric effect falls into two parts, the permanent mesomeric (*M*) effect present in the ground state, and the additional electronic (*E*) effect, which represents a time-variable polarisability contribution operative in reacting molecules and reaches its maximum in the transition state. The time-variable counterpart of the inductive effect, the inductomeric effect, is likely to be small and is neglected. On this basis, the effect of a phenyl substituent is described as $-I,\pm T$. The $-I$ effect arises from the fact that the constituent atoms of a phenyl substituent, like those of any covalently unsaturated group, have less than their normal share of bonding electrons (the double-bond or π-electrons being less " bonding " than the single-bond or σ-electrons). The $-I$ effect would be expected to increase with increasing unsaturation in the sequence vinyl < phenyl < naphthyl < anthryl, phenanthryl, but to be much less than proportional to the number of double bonds in the substituent, since the additional unsaturation will be further and further removed from one particular point, and since the *I* effect, being mainly electrostatic in origin, rapidly decreases in the distance. The $\pm T$ effect of a phenyl substituent arises from the fact that it can partake of resonance forms of the type  or of the type  and that the polarity will be mainly determined by X. Since the number of possible polar forms increases in the sequence phenyl < 2-naphthyl < 1-naphthyl < 9-phenanthryl < 9-anthryl, the $\pm T$ effects would be expected to increase in that order. The actual reactivity sequence will depend on a combination of the *I* and *T* effects. In a reaction facilitated by electron-recession, the $-I$ and $-T$ effects will reinforce each other and the expected reactivity sequence is the same as for the *T* effects. In a reaction requiring electron-accession on the other hand, the $-I$ and $+T$ effects will oppose each other and the actual sequence will depend on the relative magnitudes of the two effects. These may vary from case to case, as with other $-I,+T$ substituents, such as the halogens. Whatever the resultant sequence, the reactivity differences will be smaller than with a reaction requiring electron-recession.

An estimate of the *I* effects alone may be derived from the dissociation constants of the arylcarboxylic acids, arylamines, and aryl-hydroxy-derivatives, if it is assumed that the $+T$ and $-T$ effects brought into play by the forward and backward reactions are of equal magnitude, so that the equilibria will be determined only by the $-I$ effects. (Detailed consideration shows that this assumption is likely to be only approximately correct.) The available data (Table IV) bear out the expected sequence of $-I$ effects, vinyl < phenyl < 2-naphthyl < 1-napthtyl < phenanthryl < anthryl. (In assessing the differences quantitatively, it must be remembered that the $-I$ effects will exert opposite effects on the rates of the forward and backward reactions, and that the effect will be magnified in the dissociation constant, which is the ratio of the two.)

TABLE IV.

Dissociation constants of aryl derivatives.

X.	X·CO$_2$H (in water) ($\times 10^5$).	X·CO$_2$H (in 60% aqueous acetone) ($\times 10^6$).	X·OH ($\times 10^{10}$).	X·NH$_2$ ($\times 10^{10}$).
(Vinyl)	5·5 [1]	—	—	—
Phenyl	6·3 [1]	2·0 [4]	1·3 [5]	3·82 [6]
2-Naphthyl	6·8 [2]	2·8 [4]	2·5 [5]	1·29 [6]
1-Naphthyl	20·3 [3]	—	—	0·84 [6]
9-Anthryl	22·6 [3]	9·0 [4]	—	—
9-Phenanthryl	—	3·7 [4]	—	—

[1] Dippy, *Chem. Reviews*, 1939, **25**, 206. [2] Derick and Kamm, *J. Amer. Chem. Soc.*, 1917, **39**, 394. [3] Lauder, *Ber.*, 1937, **70**, 1288. [4] This paper (see Experimental). [5] Eisenbrand, *Z. physikal. Chem.*, 1929, *A*, **144**, 441. [6] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

An estimate of the differences in M effects should be obtainable from dipole moments, since these will be determined by the sum of the $-I$ and $\pm M$ effects. From a careful consideration of the moments of 1- and 2-chloronaphthalene, Hampson and Weissberger (*J.*, 1936, 393; cf. Ketelaar and Oosterhout, *Rec. Trav. chim.*, 1946, **65**, 448) deduced that there is a greater mesomeric effect in the 1- than in the 2-naphthyl derivative, but in general the interpretation of dipole moments in polycyclic derivatives is highly complicated owing to vectorial factors (cf. Bergmann and Hershberg, *loc. cit.*; Vassiliev and Syrkin, *Acta Physicochim.*, 1941, **14**, 414).

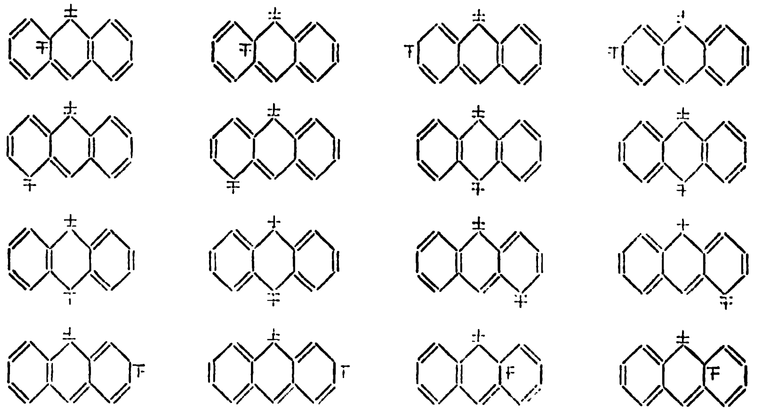
Turning again to the reactivity data in Table III, we see that the estimated differences in the rates of electrophilic substitution of the parent hydrocarbons are considerable and follow the expected sequence of $+T$ effects. In this case, therefore, the latter appear completely to outweigh the $-I$ effects. Amongst the side-chain reactions, the oxotropic rearrangement of the 1-aryl-3-methylallyl alcohols and the neutral hydrolysis of the arylmethyl bromides are facilitated by electron accession (type A; Ingold and Rothstein, *J.*, 1928, 1217), while the prototropic rearrangement of the 1-phenyl-3-arylmethyleneazomethines and the alkaline hydrolysis of the methyl naphthoates require electron recession (type B). As far as can be judged, all four reactions display the expected sequence vinyl < phenyl < 2-naphthyl < 1-naphthyl < 9-anthryl, showing that for these derivatives the $+T$ again outweigh the $-I$ effects in type A reactions. In each case, the differences in rate constants for the different aryl derivatives are remarkably small, in relation both to the effects of other substituents and to nuclear substitution. Thus, oxotropic rearrangement is known to be highly sensitive to substituent effects, *p*-methyl and *p*-methoxyl substituents attached to a phenyl group producing approximately 10- and 100-fold increases in rate, respectively (Braude and Stern, *J.*, 1947, 1096), yet a 9-anthryl as compared with a phenyl substituent only results in an approximately 5-fold increase, and the effects of the other polycyclic substituents studied are even smaller. The same applies to the other side-chain reactions, with the exception of the ammonolysis of aryl acetates where special factors are believed to be involved. The smaller reactivity differences in the side-chain as compared with the nuclear reactions may be due to the fact that, whereas the M effect must necessarily be the same in both types, the additional E effect may be much less prominent in the former than in the latter, as first suggested, in a different connection, by Bird and Ingold (*J.*, 1938, 918). This suggestion is also borne out by comparative data for a *p*-methyl substituent attached to a phenyl group; whereas in oxotropy the rate increase is about 10-fold, it is about 25-fold in nuclear nitration (Benford and Ingold, *J.*, 1938, 929) and about 400-fold in nuclear halogenation (Robertson, Johnston, and De La Mare, *loc. cit.*; Berliner and Bondhus, *J. Amer. Chem. Soc.*, 1946, **68**, 2355; 1948, **70**, 854).

In both side-chain oxotropy and side-chain prototropy, the rates of reaction of the 9-phenanthryl derivatives are unexpectedly small. This is unlikely to be due to any steric effect, since this should be even more pronounced with the 9-anthryl derivative, whereas the reactivity of the latter shows a quantitative linear correlation with the phenyl and naphthyl derivatives (see below), despite the fact that ultra-violet light absorption properties indicate that steric inhibition of resonance occurs in the rearranged isomer (Braude, Fawcett, and Newman, preceding paper). It is of course possible that steric hindrance plays a part in determining the side-chain reactivity of all the polycyclic derivatives, but nevertheless it does not readily explain the *relatively* low reactivity of the 9-phenanthryl derivatives, which therefore appears to be truly electronic in origin. If this deduction be correct, it can have only one explanation, namely, that the M effect of the phenanthryl group is unexpectedly small, smaller than that of the naphthyl and, probably, the phenyl group. In nuclear reactions, where the additional E effect is brought into play, this will not be apparent, but in side-chain reactions, where the E effect is weak, this will result in low reactivity; in type A reactions the $-I$ effect will not be sufficiently compensated by the $+M$ effect, and in type B reactions, the $-I$ effect will not be sufficiently enhanced by the $-M$ effect. The reason for the supposed abnormally small $\pm M$ effect of the phenanthryl group is not clear; it may be due to the two-directional polarisation consequent upon the " angular " arrangement of the benzene nuclei.

(3) *Quantitative Theory.*—(*a*) *Valence-bond method.* A simple approach to a quantitative or semi-quantitative theory of reactivity in polycyclic systems was outlined by Pauling (" The Nature of the Chemical Bond," Cornell, 1940), who pointed out that the reactivities of naphthalene in the 1- and the 2-position can be dicussed in terms of the respective numbers (n) of possible self-polarised structures; 7 self-polarised structures may be written containing a formal charge in the 1-position, and only 6 structures with a formal charge in the 2-position. This treatment can readily be extended to the comparison of the reactivities of different systems; thus $n = 3$

for a phenyl group, *n* = 16 for a 9-anthryl group and *n* = 13 for a 9-phenanthryl group. The 16 structures for a 9-anthryl group are shown below.

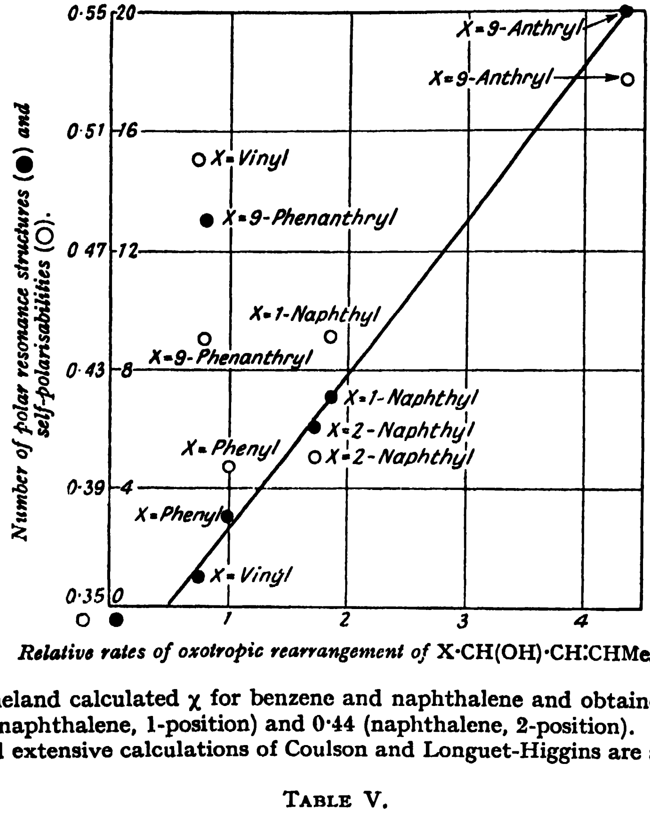
Self-polarised resonance structures of anthracene with a formal charge in the 9-position.



In the unsubstituted parent hydrocarbons, contributions from resonance forms of opposite polarity cancel each other, and the electron density is the same on each carbon atom; but under the influence of an attacking reagent, a particular polarity will be favoured and the polarisability or electromeric effect will be greater, the larger is *n*. In a substituted hydrocarbon, on the other hand, the substituent will result in a permanent mesomeric polarisation (which appears to be of prime importance in determining side-chain reactivity) and it is reasonable to suppose that, in comparing the effect of the same substituent in different hydrocarbons, the magnitude of the mesomeric effects, as well as of the electromeric effects, will run parallel to *n*. The quantitative correlation between heterolytic reactivity and the number of possible self-polarised structures depends on the following additional assumptions, amongst others : (1) The contributions of the different self-polarised structures of one system are approximately equal; (2) the excess (or deficiency in) electron-density is proportional to the number of contributing structures carrying a formal charge at a given point; (3) in side-chain reactions the resonance polarisation (mesomeric effect) outweighs any inductive effects. The figure shows a plot of the rate constants for the oxotropic rearrangements of the 1-aryl-3-methylallyl alcohols against *n*; a straight line is obtained except for the 9-phenanthryl derivative. The value for the corresponding vinyl derivative, 1-vinyl-3-methylallyl alcohol is included for comparison, and falls accurately on the linear plot. On the whole, therefore, the simple valency-bond resonance treatment is very successful in the present case, but it indicates an abnormally small *M* effect for the 9-phenanthryl group, a conclusion already reached from qualitative considerations. Probably assumptions (1) and (2) do not hold in this case.

A different type of valency-bond treatment, which takes into account contributions from excited (Dewar) structures containing ineffective bonds, has recently been developed by a number of workers (Svartholm, *Arkiv Kemi, Min. Geol.*, 1942, **15**, *A*, 1; Daudel and Pullman, *J. Phys. Radium*, 1946, **7**, 59, 74, 105; Pullman, *Experientia*, 1946, **2**, *A*, 364; Daudel and Daudel, *J. Chem. Physics*, 1948, **16**, 639). The contributions of Dewar-type structures are thought to be considerable, and the density of spin-paired, but ineffectively bonded, π-electrons is expressed as a "*charge totale* or free valency number" (Q), which should be a measure of heterolytic reactivity. The soundness of the underlying mathematical principles has been criticised by Moffitt (*Trans. Faraday Soc.*, 1949, **45**, 373), who calculates a different parameter, the "residual affinity" (r) which is a measure of the initial ease of displacement of an electron on a particular atom (Table V). Both Q and r run parallel, as they theoretically must, to the number *n*, of self-polarised structures, but the plots of k against Q or r are not linear. The scanty kinetic data so far available, therefore, indicate that contributions from polar structures are more important than contributions from Dewar structures, but further experimental evidence is clearly required on this point.

(*b*) *Molecular-orbital method.* A more elaborate approach to a quantitative theory of reactivity was initiated by Wheland and Pauling (*J. Amer. Chem. Soc.*, 1935, **57**, 2086) and has recently been greatly developed by Coulson and Longuet-Higgins (*Trans. Faraday Soc.*, 1947, 48, 87; *Proc. Roy. Soc.*, 1947, *A*, 191, 39; 192, 16; *Sci. J. Roy. Coll. Sci.*, 1948, 18, 13; *J.*, 1949, 971). Here the electron densities are calculated by the method of molecular orbitals, assuming that the only forces acting on the π-electrons are the exchange forces between paired electrons and the Coulomb fields of the constituent atoms. In unsubstituted aromatic hydrocarbons, the π-electron densities on each carbon atom are unity, but heterolytic reactivity is expressed by the self-polarisabilities (χ) which are a measure of the change in electron density (expressed in terms of the resonance intergral β of a π-electron pair) produced by a change in the electrostatic field.



Relative rates of oxotropic rearrangement of X·CH(OH)·CH:CHMe.

Pauling and Wheland calculated χ for benzene and naphthalene and obtained the values 0·40 (benzene), 0·40 (naphthalene, 1-position) and 0·44 (naphthalene, 2-position). The results of the more refined and extensive calculations of Coulson and Longuet-Higgins are shown in Table V.

TABLE V.

Theoretical quantities related to heterolytic reactivity.

	Number of polar resonance structures (*n*).	" Charge totale." (*Q*).[1]	" Self-polar-isabilities" (χ).[2]	" Residual affinities" (*r*).[3]
(Vinyl)	1	—	0·500	—
Phenyl	3	0·073	0·398	−0·246
2-Naphthyl	6	0·097	0·405	−0·220
1-Naphthyl	7	0·123	0·443	−0·206
9-Phenanthryl	13	—	0·442	—
9-Anthryl	20	0·25	0·526	−0·174

[1] Daudel and Daudel, *J. Chem. Physics*, 1948, 16, 639. [2] Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, 192, *A*, 16; *J.*, 1949, 971; Longuet-Higgins, *Sci. J. Roy. Coll. Sci.*, 1948, 18, 13. [3] Moffitt, *Trans. Faraday Soc.*, 1949, 45, 373.

It will be seen that χ again runs parallel, as it theoretically must, to the number *n* of simple self-polarised structures, but the quantitative relationships are somewhat different for the two parameters. Thus, whereas the values of *n* indicate, in agreement with experiment, that the difference in heterolytic reactivity between benzene and naphthalene should be greater than the difference in reactivity between the 1- and the 2-position in naphthalene, the values of χ predict the reverse relationship. Again, it seems reasonable to suppose that the polarisability not only of the parent hydrocarbons under the influence of a reagent, but also of the permanent polarisation of a series of hydrocarbon derivatives carrying the same substituent should be directly

related to χ. The figure shows that the plot of the rate constants for the oxotropic rearrangements of the 1-aryl-3-methylallyl alcohols against χ departs considerably more from the linear, however, than the plot of *k* against *n*. As before, the value of *k* for the phenanthryl derivative shows a particularly large deviation.

EXPERIMENTAL.

Materials.—The carbinols are described in the preceding paper. The aryl carboxylic acids for dissociation-constant measurements were crystallised from ethanol and had the m. p.s given in parentheses: benzoic (121°), 2-naphthoic (184°), 9-anthroic (217°), and 9-phenanthroic acid (256°). Dioxan and acetone were purified as previously described (Braude, *J.*, 1948, 1971).

Kinetic Measurements.—The technique of kinetic measurements previously described has been further simplified and improved by employing a Beckman DU photoelectric spectrophotometer for the spectrometric assay. This undoubtedly renders the method one of the most convenient and accurate for measuring the rates of organic reactions.

The appropriate amount (10—50 mg.) of carbinol was weighed into a short glass capsule, moistened with one or two drops of dioxan, and added to 25 ml. of reaction medium contained in a special reaction vessel (Part V, *loc. cit.*) immersed in a thermostatically controlled bath. At suitable time intervals, 1 ml. of solution was withdrawn and immediately diluted to 10 or 50 ml. with absolute ethanol and 1 ml. of 0·01M-aqueous potassium hydroxide. The intensity of absorption of the diluted solution at the chosen wave-length was then determined in a 1-cm. cell, the same solvent being used in the comparison cell.

Normally, one of the maxima exhibited by the rearranged carbinol was chosen for intensity determinations. A slightly different procedure had to be adopted in the case of the 9-anthryl derivative, as solutions of the rearranged carbinol are so strongly fluorescent that the maxima do not obey the Beer–Lambert law even at low extinctions (cf. Braude, Fawcett, and Timmons, *J.*, in the press); moreover, the differences in intensities of the maxima of the two isomers are in any case rather small. It was possible, however, to find empirically a wave-length (2650 A.) on a part of the curve at which the intensity was directly proportional to the concentration of rearrangement product and good first-order rate constants were obtained in this way.

Rearrangements of X·CH(OH)·CH:CHMe *in aqueous dioxan*–0·01M-*hydrochloric acid at* 30°.

c_{ROH} = carbinol concentration (% w/v); c_S = dioxan concentration (% v/v).

(I) X = 1-Naphthyl, c_{ROH} = 0·197, c_S = 60.

Time (mins.)	0	15·0	20·0	25·0	30·0	35·0	420	
$E^{1\%}_{1\,\text{cm.}}$ (at 2960 A.)	119	248	279	303	326	345	440	
10^4k (min.$^{-1}$)	—	345	344	341	346	347	—	(Mean) 345

(II) X = 1-Naphthyl, c_{ROH} = 0·192, c_S = 80.

Time (mins.)	0	28·0	45·1	65·0	85·1	106·0	1080	
$E^{1\%}_{1\,\text{cm.}}$ (at 2960 A.)	119	221	268	307	340	360	451	
10^4k (min.$^{-1}$)	—	132	132	129	129	123	—	(Mean) 129

(III) X = 2-Naphthyl, c_{ROH} = 0·0365, c_S = 60.

Time (mins.)	0	15·0	23·0	30·2	37·0	45·0	720	
$E^{1\%}_{1\,\text{cm.}}$ (at 2455 A.)	123	1040	1410	1640	1855	2010	2600	
10^4k (min.$^{-1}$)	—	310	317	318	323	319	—	(Mean) 318

(IV) X = 2-Naphthyl, c_{ROH} = 0·0360, c_S = 80.

Time (mins.)	0	20·0	40·0	60·0	80·2	100	1080	
$E^{1\%}_{1\,\text{cm.}}$ (at 2455 A.)	123	704	1140	1465	1710	1970	2650	
10^4k (min.$^{-1}$)	—	132	128	125	123	129	—	(Mean) 127

(V) X = 9-Anthryl, c_{ROH} = 0·0371, c_S = 60.

Time (mins.)	0	6·1	8·0	10·5	11·5	13·0	100	
$E^{1\%}_{1\,\text{cm.}}$ (at 2650 A.)	165	230	246	255	269	281	336	
10^4k (min.$^{-1}$)	—	780	800	785	815	820	—	(Mean) 800

(VI) X = 9-Anthryl, c_{ROH} = 0·0372, c_S = 80.

Time (mins.)	0	10·0	15·0	20·0	26·0	31·0	420	
$E^{1\%}_{1\,\text{cm.}}$ (at 2650 A.)	165	207	224	242	255	266	325	
10^4k (min.$^{-1}$)	—	308	308	329	318	321	—	(Mean) 316

(VII) X = 9-Phenanthryl, c_{ROH} = 0·191, c_S = 60.

Time (mins.)	0	20·0	28·0	36·1	45·0	55·0	720	
$E^{1\%}_{1\,\text{cm.}}$ (at 3030 A.)	62	174	213	250	277	301	504	
10^4k (min.$^{-1}$)	—	146	149	153	148	147	—	(Mean) 148

(VIII) X = 9-Phenanthryl, c_{ROH} = 0·185, c_S = 80.

Time (mins.)	0	50·0	70·1	90·0	110	130	1080	
$E^{1\%}_{1\,\text{cm.}}$ (at 3030 A.)	62	190	230	265	295	321	511	
10^4k (min.$^{-1}$)	—	67·1	66·0	66·1	66·0	66·1	—	(Mean) 66·3

The rate constants were calculated from the expression $k = 2{\cdot}3 \log[(a - x_0)/(a - x)]/t$, where t = time in minutes, x_0 = initial intensity, x = intensity at time t, and a = final intensity at the wave-length chosen. The final intensities a were identical within experimental error (±2%) with the intensities at the same wave-lengths of the pure rearranged carbinols. Some typical runs are reproduced above. The majority of the k values given in Table I are averaged from several runs.

Energies of activation ($E_{\text{Arr.}}$) were computed graphically from the plots of rate constants against $1/T$. The plots were satisfactorily linear. Probability factors refer to specific rate constants (k/c_A) and were calculated from the expression $\log A = 0{\cdot}723E_{\text{Arr.}} + \log(k_{30^\circ}/c_A) - 1{\cdot}78$, where c_A = acid concentration = 0·01M.

Determination of Dissociation Constants.—The dissociation constants of the aryl carboxylic acids were determined spectrophotometrically in 60% (by vol.) aqueous acetone, bromophenol-blue being used as indicator. (For the general principles of colorimetric and spectrometric acidity measurements, see Brode, *J. Amer. Chem. Soc.*, 1924, **46**, 581; Braude, *J.*, 1948, 1971; Stock and Davies, *J.*, 1949, 1371.) High accuracy was not essential for the present purpose and a simple procedure was adopted in which the hydrogen-ion concentration of suitable carboxylic acid solutions was determined by direct interpolation of the indicator ratios with those of dilute hydrogen chloride solutions. Since the commercial bromophenol-blue employed is not a pure substance and also since it is somewhat unstable in solution, absorption intensities are not recorded in absolute units, but as extinctions (E) of neutral and acid solutions of identical indicator concentrations (*ca.* 0·02%). E values were determined at the maximum (5850 A.) in a 1-cm. cell, a Beckman DU photoelectric spectrophotometer being used. In the following table, E_N refers to the neutral solutions and E_A to the acid solutions, c is the acid concentration in g.-mols./l., and I is the indicator ratio given by $(E_N - E_A)/E_A$.

Acid.	$10^4 c$.	E_N.	E_A.	I.	10^5 [H⁺].	f.	$10^6 K_A$.
HCl	0·4	0·715	0·450	0·59	4	—	—
,, ...	0·6	0·715	0·195	2·7	6	—	—
,, ...	0·8	0·715	0·121	4·9	8	—	—
,, ...	1·0	0·715	0·082	7·7	10	—	—
Benzoic	19	1·449	0·330	3·4	6·6	0·90	2·0
2-Naphthoic	10·9	1·449	0·413	2·5	5·8	0·92	2·8
9-Anthroic	5·7	1·463	0·294	3·95	7·1	0·94	9·0
9-Phenanthroic	9·4	1·449	0·364	3·0	6·2	0·92	3·7

On plotting the acid concentration c against I for the hydrochloric acid solutions, a straight line is obtained in the range I = 0·5—5·0 which is also that of highest accuracy in I (Braude, *loc. cit.*). Since hydrogen chloride is almost completely dissociated in 60% aqueous acetone (cf. Braude and Stern, *J.*, 1948, 1978), and since the ionic-strength correction (Stock and Davies, *loc. cit.*) is negligible at the low acid concentrations employed, c_{HCl} can be equated to the hydrogen-ion concentration [H⁺]. The hydrogen-ion concentration of the carboxylic acid solutions could then be evaluated directly from the I–[H⁺] plot. The data show that, under the conditions chosen, the carboxylic acids are all less than 15% dissociated and the dissociation constants K_A are given by $K_A = f^2[\text{H}^+]^2/(c - [\text{H}^+])$. The activity coefficients f were calculated from the expression $\log f = -1{\cdot}1\sqrt{c}$, based on the limiting Debye–Hückel equation which should be sufficiently applicable at the low ionic strengths involved. The dielectric constant of 60% aqueous acetone at 25° was taken as 48 (Akerlöf, *J. Amer. Chem. Soc.*, 1932, **54**, 4125).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

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160. *The Kinetics of Aromatic Halogen Substitution. Part VII. Nitrosobenzene and Azobenzene.*

By P. W. ROBERTSON, T. R. HITCHINGS, and G. M. WILL.

The reaction between bromine and nitrosobenzene in carbon tetrachloride shows a period of induction, and in the presence of hydrogen bromide proceeds at a rate 10^{10} times as fast as the bromination of benzene under the same conditions. Hydrogen bromide is consumed in the process, and is also found to react with nitrosobenzene in carbon tetrachloride by a very fast reaction. A mechanism is proposed involving, as the first stage, the formation of the compound PhNBr·OH, which after rearrangement further reacts with bromine to form the various products. Azobenzene gives a measurable reaction with bromine in acetic acid at 35° only in the presence of hydrogen bromide, and here also the first stage appears to involve the preliminary addition of hydrogen bromide. Water decelerates this reaction to an unmeasurable rate in 20% aqueous acetic acid, and in the same mixed solvent chlorine reacts with azobenzene at a slow rate, five times as fast as with benzene.

NITROSOBENZENE on bromination in carbon disulphide readily forms *p*-bromonitrosobenzene to the extent of as much as 40%, together with other compounds, of which *pp'*-dibromoazoxybenzene is present in the greatest amount (Ingold, *J.*, 1925, 513); likewise in benzene solution there is rapid formation of *p*-bromonitrosobenzene (Le Fèvre, *J.*, 1931, 810). This easy *para*-bromination of nitrosobenzene is unexpected, as the nitroso-group, although it can exert a $+T$ effect, has $-T$, $-I$ characteristics also; its dipole moment (3·2 D., directed away from the benzene ring) is greater than that of a *tert.*-alkyl nitroso-compound, a condition that usually determines *meta*-substitution and a slow rate of reaction. It has been suggested that the reaction taking place is the bromination of a dimer (Hammick *et al.*, *J.*, 1934, 29). We find from light-absorption measurements that there is very little difference in the intensity of colour of solutions of nitrosobenzene in acetic acid (in which the solute is unimolecular), carbon disulphide, and carbon tetrachloride, over the concentration range, M/40—M/160, at 16°. It seems probable that the concentration of the dimer in these solutions is too small to cause the rapid reactions that are observed, even if it should have a constitution favourable for *op*-substitution.

Nitrosobenzene reacts with bromine in carbon tetrachloride at a variable rate, and on examination of the solutions in a dim light a period of induction may sometimes be observed, the start of the reaction being indicated by a cloudiness spreading through the liquid. With added hydrogen bromide, there is no period of induction, and the reaction becomes moderately reproducible, a reaction mixture containing nitrosobenzene (M/80), bromine, (M/80), and hydrogen bromide (M/400) having a half-reaction time of three minutes at 17°; rising bimolecular coefficients indicate the autocatalytic nature of the process.

% bromine absorption (x)	20	30	40	50	60	70
k_2 (min.$^{-1}$ g.-mol.$^{-1}$ l.)	20	23	25	27	30	35

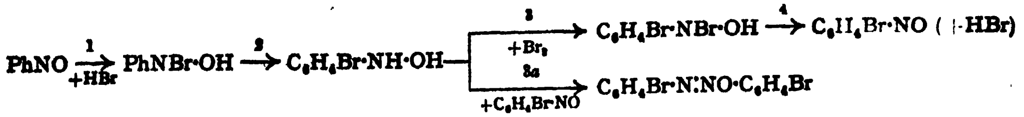
In these experiments, the reaction was stopped by shaking the solution with aqueous potassium iodide, and it was established that iodine which entered the organic phase during the titration was not acting as a catalyst, though the opposite is usually found for bromination in carbon tetrachloride.

It is instructive to compare the rates of bromination of nitrosobenzene and mesitylene. The latter has been shown to halogenate about 10^8 times faster than benzene (*J.*, 1943, 276), and therefore about 10^9 times faster than chlorobenzene (*J.*, 1948, 100). Catalysis by hydrobromic acid of its bromination (reactants, M/40, in carbon tetrachloride at 25°) results in only a threefold increase of rate with M/10-catalyst, the initial rate under these conditions being given by $k_2(x = 10) = 0{\cdot}3$. Thus nitrosobenzene, which brominates only slowly in the absence of a catalyst, reacts with bromine some 100 times as rapidly as mesitylene (and hence perhaps 10^{10} times as rapidly as benzene), when hydrobromic acid is added, despite the expected deactivation of the aromatic ring by the nitroso-group. These facts indicate that the bromination of nitrosobenzene proceeds by some mechanism other than that of normal electrophilic substitution. An atom-chain mechanism appears to be excluded as the rate of reaction is insensitive to light, and is the same in a nitrogen atmosphere as in the presence of air, the oxygen of which might oxidise the hydrogen bromide and initiate chains.

In another series of experiments in carbon tetrachloride the rates were measured by stopping the reaction with a dilute solution of sodium peroxide, and titrating the bromide ion produced. Part of the total bromine could not be accounted for, owing to the fact that some of the bromine of the hydrogen bromide formed had entered the benzene ring. The reaction, measured in this way, was found to proceed at a similar fast rate, and with M/80- (and also M/40-) reactants the disappearance of hydrogen bromide amounted to about 45% of that which should have been produced by substitution.

The reaction between nitrosobenzene and hydrogen bromide was examined kinetically. With M/80-reactants in carbon tetrachloride at 17°, the reaction proceeded rapidly to 50% absorption (0·7 minute), and stopped with about 70% absorption of the hydrogen bromide. The products of this reaction were found by Bamberger *et al.* (*Ber.*, 1899, 32, 210) to be *p*-bromophenylhydroxylamine, *pp'*-dibromoazoxybenzene, *p*-bromoaniline, and 2 : 4-dibromoaniline. As *p*-bromophenylhydroxylamine is an intermediate product, we have also studied the reaction between phenylhydroxylamine and bromine. With M/40-reactants in carbon tetrachloride at 17°, 80% of the bromine was absorbed in about 0·7 minute, and a further 5% more slowly. The products of this reaction included a dark, slightly soluble material, and *p*-bromonitrosobenzene.

The results of these various rate-measurements, and the experiments by Ingold and by Bamberger, provide evidence for establishing a probable mechanism for the bromination of nitrosobenzene. The reaction begins by the addition of hydrogen bromide to the nitrosobenzene, and then proceeds as now indicated, all the changes being rapid ones.

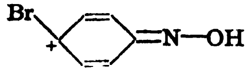


$$\mathrm{PhNO} \xrightarrow[+\mathrm{HBr}]{1} \mathrm{PhNBr{\cdot}OH} \xrightarrow{2} \mathrm{C_6H_4Br{\cdot}NH{\cdot}OH} \left\{ \begin{array}{l} \xrightarrow[+\mathrm{Br_2}]{3} \mathrm{C_6H_4Br{\cdot}NBr{\cdot}OH} \xrightarrow{4} \mathrm{C_6H_4Br{\cdot}NO}\ (+\mathrm{HBr}) \\ \xrightarrow[+\mathrm{C_6H_4Br{\cdot}NO}]{3a} \mathrm{C_6H_4Br{\cdot}N{:}NO{\cdot}C_6H_4Br} \end{array} \right.$$

Stage 2 in this scheme is analogous to the conversion of *N*-bromoacetanilide into the *p*-bromo-derivative; stages 3 and 4 are to be expected as a similar change takes place on the bromination of phenylhydroxylamine, and stage 3*a* takes place by condensation of the *p*-bromophenylhydroxylamine with *p*-bromonitrosobenzene. An alternative side-reaction proceeding to a limited degree appears to be, $\mathrm{C_6H_4Br{\cdot}NH{\cdot}OH} \longrightarrow \mathrm{C_6H_3Br(OH){\cdot}NH_2} \longrightarrow \mathrm{C_6H_3Br(OH){\cdot}N{:}N{\cdot}C_6H_4Br}$, as we have found that on treating the reaction product with aqueous alkali a yellow solution is obtained. This is consistent with the intermediate formation of *p*-bromophenylhydroxylamine, as its change to 4-bromo-2-hydroxyphenylhydroxylamine is known to take place.

With equimolecular amounts of nitrosobenzene and bromine about 10% of the bromine remains unconsumed, and since about 45 molecules % of hydrogen bromide are used in proceeding by route 3*a*, about one quarter of the total bromine must take part in the formation of more highly substituted products. As, according to Bamberger, *p*-bromoaniline is produced by the action of hydrogen bromide on nitrosobenzene, this would be brominated to form tribromoaniline. Another change requiring more bromine is, $\mathrm{C_6H_4Br{\cdot}NBr{\cdot}OH} \longrightarrow \mathrm{C_6H_3Br_2{\cdot}NH{\cdot}OH} \longrightarrow \mathrm{C_6H_3Br_2{\cdot}NO{\cdot}N{\cdot}C_6H_4Br}$, and tribromoazoxybenzene has been identified as a product (Hammick *et al.*, *loc. cit.*).

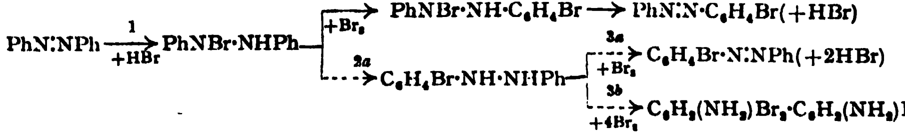
The reactivity of the bromine in *p*-bromonitrosobenzene has been discussed in connexion with the anomalous bromination of nitrosobenzene. This bromo-compound reacts with silver nitrate in acetic acid solution not only more rapidly than *p*-bromonitrobenzene but even more rapidly than picryl bromide (Le Fèvre, *loc. cit.*). Here also a reaction involving initial addition to the nitroso-group is not excluded, or it may be possible that the reactive molecule is



Azobenzene, on monobromination in acetic acid, forms *p*-bromoazobenzene (Janovsky and Erb, *Ber.*, 1886, **19**, 2156; 1887, **20**, 357; Burns, McCombie, and Scarborough, *J.*, 1928, 2928). We have now made a kinetic study of this reaction. A freshly prepared solution of M/40-bromine in acetic acid did not react with M/40-azobenzene (at 35°) during 16 hours. If this bromine solution is kept a fortnight or illuminated for several hours (both of which procedures have been found to cause the formation of a small amount of hydrogen bromide), or if hydrogen bromide is added, the reaction then proceeds. In the presence of sodium acetate or water, the reaction is inhibited. The bromination of azobenzene can be examined only with small amounts of hydrogen bromide, as this causes the formation of an insoluble salt, $\mathrm{PhN{:}NPh,HBr_3}$, and for this same reason the reaction can be followed kinetically only during the initial stages under the selected experimental conditions. The rates determined with M/40-azobenzene and M/40-bromine at 35°, in acetic acid solution which contained (*ca.* M/1000-) hydrogen bromide and varying amounts of added water, are :

H_2O (%)	0	10	25
k_2 ($x = 5$)	0·05	0·0040	~0

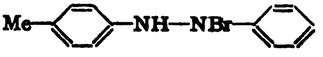
The effect of water on normal electrophilic substitution is to cause a considerable increase in the rate of reaction. It is evident that in the bromination of azobenzene a special mechanism operates involving the participation of hydrogen bromide. It was further found that hydrogen bromide very slowly added to azobenzene, giving a product in which the bromine no longer reacted with silver nitrate. It is therefore proposed that the first stage in the bromination of azobenzene proceeds by the addition of hydrogen bromide :



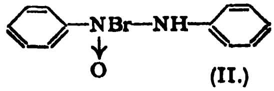
$$\mathrm{PhN{:}NPh} \xrightarrow[+\mathrm{HBr}]{1} \mathrm{PhNBr{\cdot}NHPh} \left\{ \begin{array}{l} \xrightarrow[+\mathrm{Br_2}]{2} \mathrm{PhNBr{\cdot}NH{\cdot}C_6H_4Br} \xrightarrow{3} \mathrm{PhN{:}N{\cdot}C_6H_4Br}(+\mathrm{HBr}) \\ \overset{2a}{\dashrightarrow} \mathrm{C_6H_4Br{\cdot}NH{\cdot}NHPh} \left\{ \begin{array}{l} \underset{+\mathrm{Br_2}}{\overset{3a}{\dashrightarrow}} \mathrm{C_6H_4Br{\cdot}N{:}NPh}(+2\mathrm{HBr}) \\ \underset{+4\mathrm{Br_2}}{\overset{3b}{\dashrightarrow}} \mathrm{C_6H_2(NH_2)Br_2{\cdot}C_6H_2(NH_2)Br_2}(+5\mathrm{HBr}) \end{array} \right. \end{array} \right.$$

As the bromination of azobenzene is very considerably faster than its reaction with hydrogen bromide, the change is considered to proceed chiefly by stages 2 and 3. Route 2*a* appears to be followed to some extent, however, and it is possible that tetrabromobenzidine, identified as a product by Mills (*J.*, 1894, 54), arises in this way, *via* a benzidine change and subsequent bromination (route 3*b*).

The theory involving the prior addition of hydrogen bromide in the bromination of azobenzene explains also the behaviour of related compounds. Under the conditions in which azobenzene is brominated, *p*-methylazobenzene does not react (Burns *et al.*, *loc. cit.*); the difference in the electronegativity of the nitrogen atoms in this compound causes the formation of the addition product (I), which, according to the scheme proposed, is unreactive, since the position *para*- to the amino-group is blocked.



(I.)

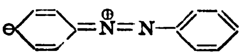


(II.)

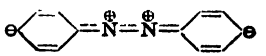
Azoxybenzene, which, like azobenzene, reacts with bromine in acetic acid only in the presence of hydrogen bromide, would give preferably the addition compound (II) and this would be substituted in the benzene ring not attached to the NO group, as is found experimentally.

The chlorination of azobenzene, like its bromination, does not proceed with a freshly prepared solution of chlorine in acetic acid, but only when hydrogen chloride is present. Water added to the acetic acid solution causes the rate to increase towards the true electrophilic rate. Such a reaction was not observed with bromine because the substitution is slower by several powers of ten than chlorination, and becomes unmeasurable. The rate of chlorination of azobenzene in 20% aqueous acetic acid at 25° (k_2 = 0·055) is about five times that for benzene (k_2 = 0·012) under the same conditions.

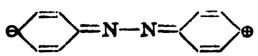
Although azobenzene, like nitrosobenzene, has lone pairs of electrons on the nitrogen atoms capable of conjugation with the aromatic ring (structures III, IV, V), such conjugation appears not to be favoured, since the C–N and N–N bond lengths in azomethane and azobenzene are almost identical (Brockway, *Rev. Modern Physics*, 1936, 8, 231; Hampson and Robertson, *J.*, 1941, 409). Such structures apparently contribute to an extremely limited extent to the polarisability of the molecule, since it has now been shown that azobenzene reacts with chlorine only a little faster than benzene, and, correspondingly, the apparently fast bromination of nitrosobenzene involves a special mechanism. The relative unreactivity of these compounds to electrophilic halogenation should be contrasted with the great reactivity of acetanilide and aniline; the former compound brominates about as rapidly as mesitylene (Part I, *J.*, 1943, 276), and therefore some 10^8 times faster than benzene.



(III.)



(IV.)



(V.)

EXPERIMENTAL.

The nitrosobenzene was prepared as required and was kept in a refrigerator before use; the different samples melted at 67°.

Typical rate measurements of bromine absorption are: M/80-PhNO + M/80-Br_2 + M/400-HBr; 8 ml. in CCl_4 at 17°; 20 ml. of KI + 20 ml. of N/80-$Na_2S_2O_3$ added; 8 ml. of this aqueous solution titrated with N/200-I_2.

Time (mins.)	0	2	5	10	12	1	3	6·5	8
Titre (ml.; average)	2·0	4·2	7·8	8·7	9·0	3·25	5·6	8·7	9·1
Bromine absorption (%)	0	27	73	84	88	15	45	83	89

These values give a smooth curve, as did other values obtained in experiments under nitrogen and under air.

A rate measurement in which bromine and hydrogen bromide were determined gave the following results:

M/80-PhNO + M/80-Br_2 + M/400-HBr; 8 ml. in CCl_4 at 17°; 10 ml. of dilute Na_2O_2 soln. were added, and 4 ml. of aqueous soln. were removed, acidified with acetic acid, and titrated with N/20-$AgNO_3$ (eosin):

Time (mins.)	0	1	2	4	6	10	20
Titre (ml.; average)	3·44	2·78	2·50	1·78	1·46	1·28	1·16
Br_2 + HBr absorption (%)	0	42	60	106	127	139	147

Other runs gave similar results, and the average of 10 runs, with reaction times 20 to 60 minutes, showed 145% absorption.

M/40-PhNO + M/40-HBr; 8 ml. in CCl_4 at 17°; titrations as in the experiment just described:

Time (mins.)	0	3	7	20
Titre (ml.)	3·1	1·2	1·1	0·9
HBr absorption (%)	0	61	65	70

M/40-PhNH·OH + M/40-Br_2; in CCl_4 at 17°.

Time (mins.)	0·7	2	8
Bromine absorption (%)	84	87	87

Azobenzene, m. p. 66—67°, and azoxybenzene, m. p. 34—35°, were used for the following measurements: M/40-Azobenzene + M/40-Br_2 + approximately M/1000-HBr at 35° in acetic acid; $x = 5, t = 42$; $x = 10, t = 100$ (at about $x = 10\%$ absorption of bromine, solid began to be deposited); in acetic acid containing 10% water, $x = 5$, $t = 500$. Other measurements, with bromine and an unknown amount of hydrobromic acid, similarly showed slower rates in aqueous than in glacial acetic acid, and also were subject to considerable retardation by added sodium acetate. M/40-Azoxybenzene + M/40-Br_2 + approximately M/1000-HBr; $x = 5$, $t = 100$. Both water and sodium acetate also reduced the rate of bromination of this compound. M/40-Azobenzene + M/40-Cl_2 in acetic acid containing 20% water at 25°, $x = 10, t = 80$.

The relative absorption by nitrosobenzene in different solvents was compared by use of a photoelectric colorimeter, for the red light of a mercury-vapour lamp. The following percentage transmissions were recorded at 16°: M/40-solution, in CCl_4, 38; in acetic acid, 36; in CS_2, 37; M/80-solution, in CCl_4, 52·5; in acetic acid, 52·5; in CS_2, 53·5.

Victoria University College,
Wellington, New Zealand.

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161. *The Kinetics of Halogen Substitution. Part VIII. Halogen Addition. Part XV. Benzyl and Allyl Chloride, Bromide, and Cyanide.*

By L. D. Swindale, B. E. Swedlund, and P. W. Robertson.

The order of reactivity, per molecule, is $PhH > Ph{\cdot}CH_2Cl > Ph{\cdot}CH_2Br > Ph{\cdot}CH_2{\cdot}CN$ for chlorine substitution, and

$$CH_2{:}CH_2 \gg CH_2{:}CH{\cdot}CH_2Cl > CH_2{:}CH{\cdot}CH_2Br > CH_2{:}CH{\cdot}CH_2{\cdot}CN$$

for bromine addition. The theories relating to these reactions are discussed.

The rates of aromatic substitution, as well as the orientation of the products, are of importance in elucidating the mechanisms involved in the process. This has been demonstrated by Ingold and his co-workers for nitration by the competitive method (*J.*, 1938, 905, 918, 929), and for chlorination, in the present series of investigations, for alkylbenzenes and halogenonaphthalenes (*J.*, 1943, 279; 1948, 100). The benzyl halides and in general compounds of the type $Ph{\cdot}CH_2X$ may also be investigated by this method. Whilst the present work was in progress there appeared a paper by Ingold and Shaw (*J.*, 1949, 575) on the relative rates of nitration of benzyl chloride and ethyl phenylacetate.

Our preliminary rate measurements of the chlorination of benzyl chloride in acetic acid solution showed variations greater than might be accounted for by experimental error. It was found further that in the presence of mercuric chloride these rates were lowered, whereas mercuric chloride accelerated the chlorination of toluene under the same conditions. The conclusion was that in the relatively very slow reaction with benzyl chloride nuclear substitution was accompanied by an atom-chain reaction involving side-chain substitution, and that the mercuric chloride acted as a chain-breaker. It was also ascertained that in the mixed solvent, 20% aqueous acetic acid, which would be expected to eliminate the chain-reaction, the ratio of the toluene and benzyl chloride rates was the same as in acetic acid containing mercuric chloride. The use of such a mixed solvent for the determination of comparative rates involves the risk, for benzyl chloride and bromide, of concomitant hydrolysis with the formation of a more reactive compound. No autocatalysis, however, could be detected in the chlorination of benzyl chloride, and in particular the per cent. absorption–time curves for benzene and benzyl chloride remained proportionate throughout the experimental range. Another possible disturbance is that in the benzyl bromide reaction there might be simultaneous substitution of bromine by chlorine. Such a reaction would be expected to proceed with acceleration, but here also there was no evidence of autocatalysis. It is known, moreover, that replacements of this type tend to take place more especially when there is considerable electron-accession to the point of attack, *e.g.*, in a compound such as *p*-$Me{\cdot}C_6H_4{\cdot}CH_2Br$.

Herewith are the relative initial rates of chlorination, in 20% water–acetic acid at 25°, of benzene and the compounds, $Ph{\cdot}CH_2X$.

PhH	$Ph{\cdot}CH_2Cl$	$Ph{\cdot}CH_2Br$	$Ph{\cdot}CH_2{\cdot}CN$
1	0·76	0·61	0·17

Accurate percentages of *o*-, *p*-, and *m*-substitution products are known for nitration, but not for chlorination of some of the compounds examined. The values for *m*-nitration are for $Ph{\cdot}CH_2Cl$ (15%), $Ph{\cdot}CH_2Br$ (7%), and $Ph{\cdot}CH_2{\cdot}CN$ (14%), and it is not to be expected that there should be a large difference for chlorination. At all events the reactions are proceeding chiefly to give *p*,*o*-chloro-compounds, and the relative rates in the foregoing table are substantially those for substitution in these positions. The relative rate of nitration of benzene to that of benzyl chloride, molecule per molecule, found by Ingold and Shaw (*loc. cit.*) was 1 : 0·302, indicating that benzyl chloride is more deactivated on nitration than on chlorination. In nitration the reagent is the ion NO_2^+, and in chlorination the chlorine molecule, and benzyl chloride with its permanent dipole is likely to hinder the approach of the positive ion more than the neutral molecule. A similar difference in reactivities was found between nitration and halogenation for aromatic compounds containing halogen in the nucleus (*J.*, 1948, 104).

Attention is now turned to the relative rates of chlorination of the three compounds $Ph{\cdot}CH_2X$. Chlorine has a greater inductive effect than bromine, but the difference between the dipole moments of $Ph{\cdot}CH_2Cl$ (1·85 D.) and $Ph{\cdot}CH_2Br$ (1·86 D.) is inconsiderable. In benzyl chloride the carbon atoms in the ring should be somewhat more deactivated than in benzyl bromide, and the superior reactivity of the chloride is consequently caused by the greater hyperconjugation of the hydrogen atoms in the chloromethyl group. Benzyl cyanide, on the other hand, has a greater dipole moment (3·52 D.), so that in this compound the deactivation must be more considerable than in the benzyl halides. The rate of chlorination, however, is not greatly inferior, so the hyperconjugation effect here must be large. This involves the weakening of the C–H bond by the CN group, and in this connection it is known that benzyl cyanide forms a sodium salt, $Ph{\cdot}CHNa{\cdot}CN$.

If groups such as chloromethyl act in aromatic substitution by a hyperconjugation effect reduced by an opposing inductive effect, they may be expected to act in a similar manner in causing halogen addition to ethylene compounds. The previously measured rates of bromine addition to the allyl halides in acetic acid solution are now compared with that of allyl cyanide, the velocities being calculated as second order coefficients at 25° for reactants at M/80 (x = 10% absorption):

$CH_2{:}CH{\cdot}CH_2Cl$	$CH_2{:}CH{\cdot}CH_2Br$	$CH_2{:}CH{\cdot}CH_2{\cdot}CN$
$k_2 = 1{\cdot}6$	$k_2 = 1{\cdot}1$	$k_2 = 0{\cdot}23$

In our earlier communication (*J.*, 1945, 131) the rate order, allyl chloride > allyl bromide, was considered to be anomalous, and it was suggested that it might have been caused by intervention of solvent molecules in the reaction; but the same rate ratio is found, not only in acetic acid and aqueous acetic acid solutions, but also for the reactions in the polar aprotic solvent chlorobenzene. In the non-polar carbon tetrachloride these rates appear to be reversed (Juvala, *Ber.*, 1930, **63**, 1998), but we find it difficult to obtain reproducible results for these compounds in this solvent, even in an atmosphere of dry nitrogen.

The allyl cyanide reaction in acetic acid solution is autocatalytic like those of the bromide and chloride owing to the formation of hydrogen bromide caused by the participation of solvent molecules. The following third order coefficients for bromine addition to allyl cyanide, reactants M/80, in acetic acid at 25°, show this effect.

x, %	10	20	30	40	50	60
k_3	20	23	28	33	40	53

Correspondingly, the reaction is largely catalysed by the lithium halides, as is seen from the initial rates, now calculated as second order coefficients:

	No catalyst.	LiCl, M/20.	LiBr, M/20.
$k_2(x = 10)$	0·23	2·4	1·2

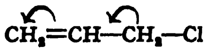
Thus for allyl cyanide, like other compounds of the type $CHR'{:}CH_2$, where R′ is a group with $+T,-I$ characteristics, LiCl is superior to LiBr as a catalyst, and as the $-I$ effect (measured by the dipole moment) is large, the catalysis is considerable (cf. *J.*, 1949, 294).

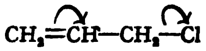
The rate of bromine addition to ethylene has now been determined by a revised technique, specially applicable to volatile reactants, and this will be described in a later communication. These measurements have, for reasons of solubility, been made in a mixed solvent composed of chloroform and carbon tetrachloride, and the rate of bromine addition to allyl bromide was measured in the same solvent. On combining these results with those shown above for the reactions in acetic acid, the following relative rates are obtained:

$CH_2{:}CH_2$	$CH_2{:}CH{\cdot}CH_2Cl$	$CH_2{:}CH{\cdot}CH_2Br$	$CH_2{:}CH{\cdot}CH_2{\cdot}CN$
1	0·019	0·013	0·0027

A comparison of this series with the one obtained for the chlorination of the benzyl compounds reveals that the order of reactivity is the same, but with a different deactivation effect in the two series. These results are consistent with the operation of a mechanism with similar electron requirements in the two reactions; but the deactivation by the CH_2X group is more considerable in the allyl compounds, where the dipole is nearer to the point of attack. The same effect has been observed for the compounds PhBr and $CH_2{:}CHBr$, since the bromine atom has the same $+T, -I$ characteristics as the CH_2X groups at present being investigated.

Just as in the compounds $Ph{\cdot}CH_2X$, there is the possibility of either *o*-, *p*-, or *m*-substitution, so also in the allyl compounds two modes of reaction, (I) and (II), are possible. According to

(I.)

$CH_2{=}CH{-}CH_2{-}Cl$

(II.)

$CH_2{=}CH{-}CH_2{-}Cl$

(I), hyperconjugation operates, whilst in (II) the mechanism is dependent on the inductive effect of the CH_2Cl group, reinforced by halogen-hyperconjugation. Certainly, Kharasch has shown that hydrogen iodide and normal hydrogen bromide addition to the allyl bromide takes place entirely by method (I); but other reagents that add to the double link may behave differently. In the case of bromine addition an approximate estimate may be made of the relative contributions of the two reactions. From a consideration of the velocities of halogen addition to $CHPh{:}CH{\cdot}CO_2H$ and $CH_2{:}CH{\cdot}CO_2H$, the same ratio of velocities being assumed for $CHPh{=}CH{\cdot}CH_2Cl$ and allyl chloride reacting as $CH_2{=}CH{\cdot}CH_2Cl$, bromine addition proceeding by method (II) would represent 12% of the total reaction. Although, therefore, bromine addition to the compounds $CH_2{:}CH{\cdot}CH_2X$ is directed chiefly by mechanism (I), just as in the compounds $Ph{\cdot}CH_2X$ halogen substitution is chiefly in the *p*,*o*-positions, there may also be an appreciable contribution from reaction by method (II).

EXPERIMENTAL.

The following compounds were used in the investigations: benzyl chloride, b. p. 178—178·5°/758 mm.; benzyl bromide, b. p. 195—197°/749 mm.; benzyl cyanide, b. p. 233—234°/760 mm.; benzene, m. p. 5°; allyl cyanide, b. p. 116—117°/753 mm.

The technique for the experiments was as previously described. Herewith is a typical bromine addition reaction:

M/80-Allyl cyanide + M/80-Br_2 in acetic acid at 25°; reaction mixture 10 ml.; 1-ml. samples titrated with KI and N/80-$Na_2S_2O_3$:

Time (mins.)	0	31·0	120	271	0	60·6	183	330
Titre (ml.)	1·99	1·86	1·39	0·88	1·99	1·67	1·16	0·79

From combined graph, $x = 10\%$, $t = 37$ mins.

Other measurements in acetic acid at 25° are: M/80-allyl cyanide + M/80-Br_2; (i) + M/20-LiCl, $x = 10$, $t = 3{\cdot}74$; (ii) + M/20-LiBr, $t = 7{\cdot}2$. In 10% aqueous acetic acid at 0°, M/80-allyl chloride + M/80-Br_2, $x = 50$, $t = 5{\cdot}4$; M/80-allyl bromide + M/80-Br_2, $x = 50$, $t = 8{\cdot}4$. In chlorobenzene at 25°, M/40-allyl chloride + M/40-Br_2, $x = 20$, $t = 76$; M/40-allyl bromide + M/40-Br_2, $x = 20$, $t = 112$.

Herewith is a typical chlorine-substitution reaction: M/2-Benzyl bromide + M/20-Cl_2 in 20% aqueous acetic acid at 25°; reaction mixture 10 ml.; 2-ml. samples titrated with KI + N/10-$Na_2S_2O_3$.

Time (mins.)	0	20·7	54·1	0	30·0	45·1	0	75·0
Titre (ml.)	1·98	1·77	1·50	1·95	1·66	1·50	1·97	1·42
Blank (ml.)	1·96	1·91	1·86	1·94	1·89	1·83	1·98	1·92

From combined graph, $x = 10\%$, $t = 25{\cdot}7$ mins.

Other results (expressed in minutes) in 20% aqueous acetic acid at 25°: M/2-Benzene + M/20-Cl_2, $x = 10$, $t = 15{\cdot}5$; M/2-benzyl chloride, + M/20-Cl_2, $x = 10$, $t = 20{\cdot}4$; M/2-benzyl cyanide + M/20-Cl_2, $x = 10$, $t = 92{\cdot}1$.

VICTORIA UNIVERSITY COLLEGE, WELLINGTON, NEW ZEALAND. [*Received, December 6th*, 1949.]

162. *Aryl-2-halogenoalkylamines. Part VI. Reactions with Certain Organic Sulphur Compounds.*

By W. C. J. Ross.

The reaction of *NN*-di-2-chloroethyl-*p*-anisidine with 2-mercaptoethanol and thiophenol in aqueous alcohol solutions of different pH has been studied. Thioethers react with arylhalogenoalkylamines to give sulphonium compounds. 4-Aryl-substituted thiazans are conveniently prepared by the reaction of aryl-di-2-halogenoalkylamines and sodium sulphide in aqueous acetone.

The reactivity of the carcinogenic and tumour-growth inhibitory arylhalogenoalkylamines towards various anions and amines was discussed in Parts III and IV (*J.*, 1949, 2589, 2824) of this series. In the present communciation some reactions of the halogenoalkylamines with certain organic sulphur compounds are described.

It has already been established in Part III that the carbonium ion derived from an "aromatic nitrogen mustard" could not react with an undissociated carboxyl group and it was thought that reaction with an undissociated thiol group was also improbable. To test this point it was necessary to allow the arylhalogenoalkylamines to react in solutions of different pH containing thiols of known dissociation constants. Since it had been found previously that aqueous acetone solutions could not be used for the quantitative study because of mercaptal formation it was necessary to determine the p*K* of typical thiols in aqueous alcoholic solution. Thiophenol and 2-mercaptoethanol were chosen as representative of aromatic and aliphatic thiols and found to have pK_a 8·05 and 10·8, respectively, in 50% alcohol.

Table I shows the results obtained when *NN*-di-2-chloroethyl-*p*-anisidine reacted with these thiols in solutions of varying pH. Under the experimental conditions all the halide will react and there is 100% excess over the amount required to react with the added thiol.

Table I.

Reaction of NN-*di-2-chloroethyl*-p-*anisidine in 50% ethanol with thiophenol and 2-mercaptoethanol. Concn. of amine* 0·01м. *Concn. of thiol* 0·01м. *Temp.* 85°. *Time 30 mins.*

Added salts.	pH change during reaction.	PhSH, % reacted.	$CH_2(SH)\cdot CH_2\cdot OH$, % reacted.
Nil	4·0—2·3	nil	nil
0·01N-HOAc + 0·01м-NaOAc	6·3—6·0	—	10
0·05м-NaOAc	8·6—6·6	90	33
0·20м-Na_2HPO_4	9·6—8·8	—	75
0·05м-Na_2CO_3	11·0—10·8	97	98

It is not easy to make experiments of this type very precise because in order to control the pH of the solution during the reaction various salts have to be added and the anions derived from each type will have characteristic competition factors towards the carbonium ions. The pH values, measured with a glass electrode, are only apparent values but as the p*K*s of the thiols were measured under identical conditions an estimate of the amount of thiol in the dissociated form can be made. Notwithstanding the imperfections of the method it is clear that the reaction with thiols is dependent on pH. In acid solutions where dissociation is suppressed there is no reaction but as the pH rises more thiol will ionise and as was expected more reaction occurs.

The results also indicate that a negatively charged sulphur atom is a powerful nucleophilic centre having a great affinity for the carbonium ion, since Table I shows considerable reaction with mercaptoethanol under conditions where only a small proportion of the thiol group will be dissociated. If this small fraction reacts rapidly with the halide then more will dissociate and eventually appreciable reaction will occur. A number of compounds which have high competition factors for carbonium ions, for example, dithiophosphates, mono- and di-thiophosphonates, thiosulphate, and dithiocarbamate (Ogston, *Trans. Faraday Soc.*, 1948, **44**, 45), are highly dissociated in solution giving ions containing, in effect, negatively charged sulphur atoms.

If only the dissociated form of a thiol can react then the competition factor for any thiol at a given pH should be $f \times F_{S^-}$, where f is the fraction of the thiol in the ionic form—an activity coefficient—and F_{S^-} is the competition factor of the ion. Some idea of the order of the competition factor of a negatively charged sulphur atom can be obtained from Ogston's figures for mustard gas. The competition factor of cysteine at pH 7 is given as $1{\cdot}2 \times 10^3$ and since cysteine has $pK_a = 10{\cdot}5$ the value of f will be about $10^{-3\cdot5}$ at pH 7·0. The value of the competition factor F_{S^-} of the ionised sulph-hydryl group will be $1{\cdot}2 \times 10^3/10^{-3\cdot5}$ or about 4×10^5. It is interesting to note that the value of the competition factor for dithiophosphate at pH 7—when f will be approximately unity—is of the same order, namely $1{\cdot}3 \times 10^5$. This high value may be compared with the values for organic-acid anions which range from 20 to 100.

Quite generally, the competition factor of a compound at any pH will be given by the expression $f_n \times F_A$ where f_n is the fraction of the substance in the reactive form at pH = n, which can be calculated from the dissociation constant, and F_A is the competition factor of the reactive form A—this will be the anion for an acid or a thiol and the free base for an amine.

In a mixed biological system at physiological pH—usually about 7·5—the extent to which any substance will react with the carbonium ion derived from an " aromatic nitrogen mustard " will be proportional to $f_{7\cdot5} \times F_A \times c$ where c is the concentration of the substance being considered. When an arylhalogenoalkylamine is administered to an animal in the relatively low dosage required to inhibit tumour growth or to induce tumour formation, in the affected cells a small amount of reagent is distributed amongst a large excess of reacting groups. It is clear that the various substances present will react in proportion to the value of the expression given above. As the mustard-gas type of compound is not an efficient inhibitor of so-called •SH enzymes (compare Dixon and Needham, *Nature*, 1946, **158**, 432) despite the high value of F_{S^-} one must conclude that the value of c for the •SH group in the tissues involved is low. Another factor is that the •SH groups in proteins are situated on the relatively short cysteine side-chains and may not be as accessible for reaction as the more exposed carboxy- and amino-groupings. Consideration of the factors mentioned above suggests that the groups most likely to react are the acid groups of proteins and the phosphoryl and aromatic type amino-groups in nucleic acids.

The isolation of *NN*-di-2-phenylthioethyl-*p*-anisidine from the reaction between *NN*-di-2-chloroethyl-*p*-anisidine and thiophenol in alkaline aqueous acetone solution at 66° was described in Part IV; the same product is obtained when the reaction is carried out at 37° and the β-*naphthyl* derivative has now been prepared in a similar manner from β-naphthyldi-2-chloroethylamine. No crystalline product has been isolated from the reaction between *NN*-di-2-chloroethyl-*p*-anisidine and mercaptoethanol but when sodium picrate is added to the product of the reaction between β-naphthyldi-2-chloroethylamine and this thiol a small quantity of the *picrate* (I) of a thiazan derivative is obtained. In Part IV it was shown that when the chlorine atom on one side-chain of an aryldihalogenoalkylamine was replaced by •NHR the rate of ionisation of the second chlorine atom was increased. It was of interest to discover the effect of replacing the first chlorine atom by •SR. Unfortunately it was not possible to ascertain this effect in as direct a way as that used in the case of the amines since the reaction has to be carried out in the presence of a buffer salt and the total halide reacting cannot be determined directly in the presence of the thiol. Table II shows the results obtained when *NN*-di-2-chloroethyl-*p*-anisidine reacted under various conditions in 50% acetone: an excess of thiol is present in this experiment so that the small loss by mercaptal formation is not significant.

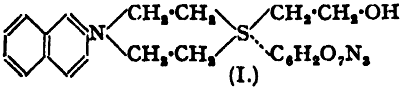

(I.)

TABLE II.

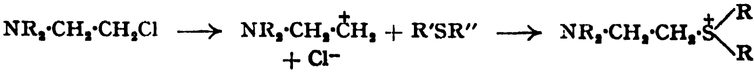
Reaction of NN-*di-2-chloroethyl*-p-*anisidine in* (a) 50% *acetone*; (b) 50% *acetone containing sodium acetate* (0·20M.); (c) *and* (d) *as* (b) *but also containing thiophenol* (0·04M.). *Concn. of amine*, 0·01M. *Temp.* 66°. *Time:* (a), (b), *and* (c), 30 *mins.*, (d) 2 *hours.*

	(*a*).	(*b*).	(*c*).	(*d*).*
H^+, %	58	6·8	76	95
Cl^-, %	58	79·5	—	—

* No extra acidity was developed if this solution was heated for a longer period, hence all the halide had reacted.

Column (*d*) indicates that the carbonium ion derived from the arylhalogenoalkylamine reacts with the thiol—and possibly to a small extent with water—and the acetate anion in the ratio 95 : 5. If one makes the reasonable assumption that thiol and acetate react in the same ratio in (*c*) then the total extent of carbonium-ion formation can be shown to be 80% in 30 minutes. It was shown in Part III that the amount of chloride ion produced when a dihalide reacted in the presence of 0·2M-sodium acetate closely represented the actual extent of the formation of the carbonium ion. Column (*b*) indicates that under the conditions chosen, 78·5% of the dihalide ionises; this is practically identical with the extent of ionisation in the presence of thiol. It can therefore be concluded that the replacement of the first chlorine atom in an aryldi(halogenoalkyl)amine by ·SR does not significantly affect the rate at which the second chlorine atom ionises.

The possible formation of sulphonium compounds by the reaction of halogenoalkylamines with thioethers is of interest because of the natural occurrence of such ethers, *e.g.* methionine. When *NN*-di-2-chloroethyl-*p*-anisidine reacts at 66° in aqueous acetone containing an excess of phenyl methyl sulphide titration of the liberated hydrogen and chloride ions indicates that about 9% of the halide has formed a sulphonium salt, the reaction of the halide with the thioether giving chloride ion but no hydrogen ion :



$$NR_2\cdot CH_2\cdot CH_2Cl \longrightarrow \underset{+\ Cl^-}{NR_2\cdot CH_2\cdot \overset{+}{C}H_2} + R'SR'' \longrightarrow NR_2\cdot CH_2\cdot CH_2\cdot \overset{+}{S}\begin{smallmatrix}R'\\R''\end{smallmatrix}$$

Approximately the same proportion of β-naphthyldi-2-chloroethylamine reacts to form sulphonium salt at 37°. In the presence of dibutyl sulphide the *p*-anisidine derivative reacts to give 26% of the sulphonium salt. The readier formation of sulphonium halides from dialkyl sulphides than from aryl alkyl sulphides has already been noted (cf. Hickinbottom, " Reaction of Organic Compounds," London, 1940, p. 114). The formation of the thiazan derivative (I) involves internal sulphonium salt formation in the monosubstitution product.

Good yields of aryl-substituted thiazans are obtained when aryldi-2-halogenoalkylamines are heated with aqueous acetone solutions of sodium sulphide. The method appears to be of general application and is a very convenient one for the preparation of such thiazans as 4-phenyl-, 4-m- and 4-p-*tolyl-*, 4-p-*chlorophenyl-*, 4-p-*methxoyphenyl-*, and β-*naphthyl-thiazan.*

There is some discrepancy in the literature concerning the properties of 4-phenylthiazan. Helfrich and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 1208, quoted in Heilbron and Bunbury's " Dictionary of Organic Compounds," London, 1943) obtained a compound, m. p. 108—111°, by the action of 2-dichloroethyl sulphide on aniline in the cold whilst Okáč (*Chem. Listy*, 1934, **28**, 227) obtained an oil when the same reactants were heated under reflux with sodium acetate and sodium carbonate in ethanol solution. Korshak and Strepikheev (*J. Gen. Chem. Russia*, 1944, **14**, 312) prepared the thiazan as a solid, m. p. 32·3—32·6°, by heating *NN*-di-2-chloroethylaniline with sodium sulphide in absolute alcohol and Cerkovnikov and Stern (*Archiv Kem.*, 1946, **18**, 12) obtained the same product by a similar method using *NN*-di-2-bromoethylaniline hydrobromide. The present results are in agreement with the findings of the Russian workers.

EXPERIMENTAL.

Determination of the pK_a *of Thiophenol and 2-Mercaptoethanol.*—2-Mercaptoethanol (780 mg.) or thiophenol (1·10 g.) was dissolved in aqueous ethanol (200 ml.; 50% by volume) and titrated with potassium hydroxide solution (0·82N. in 50% ethanol). The pH of the solution was measured after each addition of alkali by use of a glass-electrode system with a Cambridge portable electrometer valve pH meter. The results for 2-mercaptoethanol were :

ml. of KOH.	% neutralisation.	pH.	pK_a.
0	0	7·1	—
1·5	11	9·9	10·8
3·0	21	10·2	10·8
4·5	31	10·4	10·8
6·0	42	10·6	10·7
7·5	53	10·8	10·8
9·0	63	11·0	10·8
10·5	74	11·4	10·9
12·0	84	12·0	—

The average pK_a value of 2-mercaptoethanol in 50% ethanol is 10·8 and the corresponding value for thiophenol is 8·05.

Reaction of NN-*Di-2-chloroethyl-*p-*anisidine with Mercaptoethanol and Thiophenol in 50% Ethanol.*—*NN*-Di-2-chloroethyl-*p*-anisidine (500 mg.), contained in a small specimen tube, was added to boiling aqueous ethanol (200 ml.; equal volumes) containing either mercaptoethanol (156 mg.) or thiophenol (200 mg.), and the mixture was heated under reflux for 30 minutes. (A thermometer in the boiling liquid registered 85°.) The cooled solution was diluted with an equal volume of water and, after the addition of glacial acetic acid (1 ml.), the amount of unreacted thiol present was determined by titration with 0·1N-iodine (starch indicator). The experiment was repeated with various salts present; Table I shows the proportion of thiol reacting under different conditions. The pH of the solution was measured before and after the reaction on a parallel run using the method alread described.

Reaction of β-Naphthyldi-2-chloroethylamine with Thiophenol.—β-Naphthyldi-2-chloroethylamine (500 mg.), thiophenol (0·5 ml.), and sodium hydroxide (5 ml.; N.) were dissolved in aqueous acetone (500 ml.; 50%) and kept at 37° for 4 days. During this time the solution became turbid and oily droplets separated. After removal of the acetone under reduced pressure the product was extracted with benzene, and the dried extract was passed through a column of activated alumina. The eluates contained *β-naphthyldi-(2-phenylthioethyl)amine* which crystallised from benzene–light petroleum (b. p. 60—80°) as prisms, m. p. 113—114° (Found : C, 74·9; H, 6·2. $C_{26}H_{25}NS_2$ requires C, 75·2; H, 6·1%).

Reaction of β-Naphthyldi-2-chloroethylamine with 2-Mercaptoethanol.—Naphthyldi-2-chloroethylamine (1·4 g.), mercaptoethanol (3 ml.), sodium hydroxide (25 ml.; N.), and 50% acetone (500 ml.) were heated under reflux for 5 hours. Removal of the acetone yielded an oil which was dissolved in aqueous methanol containing picric acid and sodium picrate. After several days a small quantity of *picrate* had separated from the solution; it recrystallised from acetone–methanol as rhombs, m. p. 200° (decomp.) (Found: C, 52·6; H, 4·2; N, 11·6. $C_{22}H_{22}O_8N_4S$ requires C, 52·6; H, 4·4; N, 11·2%).

Reaction of NN-*Di-2-chloroethyl*-p-*anisidine with Thiophenol in* 50% *Acetone Solution at* 66°.—*NN*-Di-(2-chloroethyl)-*p*-anisidine (500 mg.), dissolved in 50% acetone (200 ml.) (*a*) alone, (*b*) containing crystalline sodium acetate (5·44 g.), or (*c*) containing thiophenol (880 mg.) and sodium acetate (5·44 g.), was heated under reflux for 30 minutes. The cooled mixture was titrated first with 0·1N-sodium hydroxide (phenolphthalein indicator) and then, after the addition of glacial acetic acid (1 ml.), with 0·1N-iodine (starch indicator). The difference between these titres represents the amount of acid produced by the reaction of the arylhalogenoalkylamine. The results are shown in Table II.

Reaction of NN-*Di-2-chloroethyl*-p-*anisidine and β-Naphthyldi*-2-*chloroethylamine with Thioethers in* 50% *Acetone Solution at* 66°.—*NN*-Di-2-chloroethyl-*p*-anisidine (500 mg.), dissolved in 50% acetone (200 ml.) containing (*a*) phenyl methyl sulphide (620 mg.) or (*b*) dibutyl sulphide (730 mg.), was heated at 66° for 30 minutes. Titration of the hydrogen ion and chloride ion indicated (*a*) H, 52·5; Cl, 57·5%: thus 5/57·5 or 8·8% of the halide reacting formed a sulphonium salt, and (*b*) H, 43·0; Cl, 58·0% : *i.e.* 15/58 or 26% of the halide yielded a sulphonium compound.

When β-naphthyldi-2-chloroethylamine (536 mg.) was dissolved in 50% acetone (400 ml.) containing phenyl methyl sulphide (620 mg.) and the solution kept at 37° for 24 hours titration indicated H, 18·5; Cl, 20·5% : the amount of halide converted into sulphonium salt being 2/20·5 or 9·8%.

Preparation of 4-Arylthiazans.—*NN*-Di-2-chloroethyl-*p*-anisidine (1 g., 4 millimols.) and sodium sulphide (5 g.) dissolved in 50% acetone (200 ml.) were heated under reflux for 2 hours. The solid which separated from the cooled mixture after removal of the acetone under reduced pressure was crystallised from light petroleum (b. p. 40—60°). 4-p-*Methoxyphenylthiazan* was obtained as long prismatic needles, m. p. 76—77° (Found: C, 63·1; H; 7·3. $C_{11}H_{15}ONS$ requires C, 63·1; H, 7·2%). Other thiazans were obtained by a similar procedure except that longer times of reaction were required for the more slowly reacting arylhalogenoalkylamines (*e.g.*, 15 hours were allowed for the reaction with *p*-chloro-*NN*-di-2-chloroethylaniline). The following have been prepared: 4-Phenylthiazan, m. p. 31°; picrate, m. p. 141° (Korshak and Strepikheev, *loc. cit.*, give m. p. 141—142°). 4-*m*-Tolylthiazan, an oil which gives a *picrate* (prisms from acetone–methanol), m. p. 187—188° (Found : C, 48·7; H, 4·4. $C_{17}H_{18}O_7N_4S$ requires C, 48·4; H, 4·3%). 4-p-*Tolylthiazan* [prisms from light petroleum (b. p. 40—60°)], m. p. 33—35° (Found: C, 68·4; H, 8·0. $C_{11}H_{15}NS$ requires C, 68·4; H, 7·8%); *picrate* (large plates from acetone), m. p. 155° after sintering at 143° and resolidifying (Found: C, 48·7; H, 4·5%). 4-p-*Chlorophenylthiazan* [prisms from light petroleum (b. p. 40—60°)], m. p. 70—71° (Found: C, 56·2; H, 5·7. $C_{10}H_{12}NClS$ requires C, 56·2; H, 5·7%). 4-β-*Naphthylthiazan* [prisms from light petroleum (b. p. 60—80°)], m. p. 82—83° (Found: C, 73·1; H, 6·7. $C_{14}H_{15}NS$ requires C, 73·2; H, 6·6%)

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THE CHESTER BEATTY RESEARCH INSTITUTE,
FULHAM ROAD, LONDON, S.W.3.

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163. *Some* 1 : 7- *and* 1 : 2 : 7-*Derivatives of Naphthalene.*

By HERBERT H. HODGSON and RAYMOND E. DEAN.

7-Bromo-1- and 8-bromo-2-naphthylamine, 1-bromo-7- and 7-bromo-1-nitronaphthalene, 1 : 7-dibromonaphthalene, the 2-halogeno-1 : 7-dinitronaphthalenes, and 7-nitronaphthalene-2 : 1-diazo-oxide, and the nitration of 7-nitro-*m*-nitrobenzenesulphon-2-naphthalide are described. The nitration of 1 : 7-dinitro-*m*-nitrobenzenesulphon-2-naphthalide occurs in the naphthalene nucleus as shown by hydrolysis of the nitration product to 1 : 5(?) : 7-trinitro-2-naphthylamine. The last compound does not form a picrate or deaminate readily.

1 : 7-DINITRO-2-NAPHTHYLAMINE is readily diazotised by Hodgson and Walker's method (*J.*, 1933, 1620), and 2-chloro-, 2-bromo-, and 2-iodo-1 : 7-dinitronaphthalene are obtained by subsequent Sandmeyer reactions. Special conditions are necessary for the preparation of 7-nitronaphthalene-2 : 1-diazo-oxide.

Nitration of 1 : 7-dinitro-*m*-nitrobenzenesulphon-2-naphthalide occurs in the naphthalene nucleus and not in the side chain, as is shown by hydrolysis of the trinitrated product to a 1 : *x* : 7-trinitro-2-naphthylamine, where *x* has not been determined but on all analogy should be the 5-position. 1 : 5(?) : 7-Trinitro-2-naphthylamine would not form a picrate, owing either to steric or more probably to the much enfeebled basic character of the 2-amino-group. Similarly, 1 : 7-dinitro-2-naphthylamine is inert towards *m*-nitrobenzenesulphonyl chloride. Attempts to deaminate the trinitro-compound by the cuprous oxide–methanol procedure, described for 1 : 7-dinitro-2-naphthylamine, were unsuccessful.

EXPERIMENTAL.

Improvements in the Preparation of 2 : 7-*Dinitronaphthalene.*—Using a modification of Hodgson and Ward's method (*J.*, 1945, 590), 3 : 6-dinitronaphthalic anhydride (20 g.) is added during *ca.* 4 minutes to boiling dry quinoline (40 c.c.) containing copper bronze (5 g.) in suspension, and then more copper bronze (5 g.) is added and boiling continued for a total period of 15 minutes. Synthetic quinoline affords a cleaner product in somewhat better yield (34%) than does coal-tar quinoline (about 23%).

Preparation of Some 1 : 7-*Derivatives of Naphthalene.*—8-*Bromo*-2-*naphthylamine*. A solution of 1-bromo-7-nitro-2-naphthylamine (2·3 g.) (Hodgson and Ward, *J.*, 1947, 327) in sulphuric acid (5 c.c.; *d* 1·84) was added to one of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84), the whole was stirred into glacial acetic acid (20 c.c.) at <20°, and stirring was continued for 30 minutes. The mixture was then added gradually to a stirred suspension of cuprous oxide (4 g.) in methanol (70 c.c.) at 55°, and the stirring continued until the solution had cooled to room temperature, whereupon the whole was poured on ice and kept overnight. The precipitate was filtered off, washed with water, 2% aqueous sodium carbonate, and again with water, and then extracted with boiling ethanol (charcoal). The extract was filtered and allowed to evaporate, whereupon 1-*bromo*-7-*nitronaphthalene* separated (1·25 g., 58% yield); it recrystallised from ethanol in orange plates, m. p. 135° (Found: N, 5·7; Br, 31·6. $C_{10}H_6O_2NBr$ requires N, 5·5; Br, 31·7%). 1-Bromo-7-nitronaphthalene (1 g.) was reduced by being heated under reflux for 3 hours with a mixture of iron powder (pin dust) (3·0 g.), ferrous sulphate (0·5 g.), and water (30 c.c.); the solid was filtered off, washed with cold water, dried, and extracted with boiling ethanol (charcoal), and the filtered extract allowed to evaporate, whereupon 8-*bromo*-2-*naphthylamine* (0·4 g.) separated and was recrystallised from ethanol; it formed pale brown rods, m. p. 74° (Found: N, 6·5; Br, 35·9. $C_{10}H_8NBr$ requires N, 6·3; Br, 36·0%).

1 : 7-*Dibromonaphthalene*. A fine suspension of 7-*bromo*-1-*naphthylamine hydrobromide* [(Found: Br, 52·6. $C_{10}H_9NBr_2$ requires Br, 52·8%), obtained as colourless needles when 7-bromo-1-naphthylamine (2·0 g.) was dissolved in hot hydrobromic acid (2·5 c.c.; *d* 1·7) and water (15 c.c.), and the solution chilled to 0°] was diazotised at 0° by the addition of sodium nitrite (1 g.) in the minimum amount of water. After 20 minutes, the clear solution was stirred into one of cuprous bromide (4 g.) in hydrobromic acid (10 c.c.; *d* 1·7) at 60° and stirring continued until room temperature was attained; the mixture was poured on to ice and kept overnight. The latter was then filtered off, washed with water, 2% aqueous sodium carbonate, and finally with water, and extracted with boiling ethanol (charcoal). The extract was allowed to crystallise, and the crystals (0·15 g.) were recrystallised from ethanol, 1 : 7-*dibromonaphthalene* being obtained in colourless needles, m. p. 61° (Found: Br, 55·7. $C_{10}H_6Br_2$ requires Br, 55·9%).

7-Bromo-1-nitronaphthalene (5·7 g) was obtained from 8-nitro-2-naphthylamine (10 g.) by the same procedure as above, and crystallised from ethanol in small pale yellow needles, m p 107° (Salkind and Filinov, *J Gen. Chem. Russia*, 1934, **4**, 979, give m. p. 110—111°) which could not be raised by repeated crystallisation (Found: N, 5·6; Br, 31·5. Calc. for $C_{10}H_6O_2NBr$: N, 5·5; Br, 31·7%). *Brit. Abs.*, 1935, 204, incorrectly describe this compound as 2-bromo-7-nitronaphthalene.

7-*Bromo*-1-*naphthylamine*. Finely powdered 7-bromo-1-nitronaphthalene (4 g.) was heated under reflux for 3 hours with iron powder (pin dust) (12 g.), crystallised ferrous sulphate (2 g.), and water (100 c.c.), the mixture was filtered cold, and the residue washed with cold water, dried, and extracted with boiling ethanol. The extract, after being boiled with animal charcoal, was filtered, and the filtrate allowed to evaporate slowly, but crystallisation was unsatisfactory. The solid obtained was dissolved in hot 5% hydrochloric acid, and, from the cooling solution, 7-*bromo*-1-*naphthylamine hydrochloride* (3·2 g.) separated in white gleaming plates, m. p. 250° (Found: HCl, 14·0. $C_{10}H_8NBr,HCl$ requires HCl, 14·1%), which darkened on exposure to light. Basification with ammonia afforded pure 7-*bromo*-1-*naphthylamine* (2·8 g.), which crystallised from ethanol in colourless needles, m. p. 52° (Found: Br, 35·8. $C_{10}H_8NBr$ requires Br, 36·0%), that became mauve-brown in air.

Preparation of Some 1 : 2 : 7-*Derivatives of Naphthalene.*—*The* 2-*halogeno*-1 : 7-*dinitronaphthalenes.* 1 : 7-Dinitrotoluene-*p*-sulphon-2-naphthalide (2·3 g.; m. p. 171°; cf. Hodgson and Ward, *J.*, 1947, 1060, who give m. p. 165—166°) was hydrolysed by dissolution in sulphuric acid (5 c.c.; *d* 1·84) and heating at 40° for 5 minutes, a solution of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84) was added, and the mixture was stirred dropwise into glacial acetic acid (20 c.c.) at <20°. After a further 30 minutes' stirring the solution was divided into three equal portions which were dealt with separately as follows: (*a*) was stirred into a solution of cuprous chloride (2·5 g.) in hydrochloric acid (25 c.c.; *d* 1·18), and, when evolution of nitrogen had ceased, the thick dark mixture was poured into iced water, and the pale yellow precipitate (0·45 g.) was kept overnight, then filtered off, and washed with water (500 c.c.), 2% aqueous sodium carbonate (150 c.c.), and water (500 c.c.), dried at 70°, and extracted with boiling ethanol (charcoal); on evaporation, the filtered extract afforded 2-*chloro*-1 : 7-*dinitronaphthalene* (0·2 g.), which recrystallised from ethanol in pale brown needles, m. p. 161° (Found Cl, 13·9. $C_{10}H_5O_4N_2Cl$ requires Cl, 14·0%): (*b*) was poured into a solution of cuprous bromide (2·5 g.) in hydrobromic acid (25 c.c. *d* 1·7), and then dealt with as in (*a*); the crude 2-*bromo*-1 : 7-*dinitronaphthalene* (0·6 g.) obtained crystallised from ethanol in yellow micro-needles (0·25 g.), m. p. 149° raised by sublimation to 155—156° (Found: Br, 27·0. $C_{10}H_5O_4N_2Br$ requires Br, 26·9%: (*c*) was stirred into a solution of potassium iodide (5 g.) in an amount of water insufficient for complete dissolution; the mixture was kept until reaction had ceased, then stirred into iced water and left overnight; the red precipitate (0·6 g.) was removed, washed with water (500 c.c.) and aqueous sodium thiosulphate (10 g. of solid in 500 c.c. of water), and dried at 70°; extraction as for (*a*) and (*b*) gave 2-*iodo*-1 : 7-*dinitronaphthalene*, which crystallised from ethanol in reddish-fawn rods, m. p. 163°, which sublimed to very pale fawn needles, m. p. 166° (Found: I, 36·7. $C_{10}H_5O_4N_2I$ requires I, 3·69%).

7-Nitronaphthalene-2 : 1-diazo-oxide. When a solution of 1 : 7-dinitro-2-naphthylamine (0·5 g.) in sulphuric acid (4 c.c.; *d* 1·84) was treated at <10° with one of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84) and the mixture stirred into a suspension of copper carbonate (3 g.) in glacial acetic acid (25 c.c.) there was an immediate precipitation of *7-nitronaphthalene-2 : 1-diazo-oxide* (0·45 g.), which was filtered off, washed three times with water (100 c.c.) and dried at 50°; it separated from ethanol in clusters of pale yellow sword-like crystals (Found: N, 19·8. $C_{10}H_5O_3N_3$ requires N, 19·5%) which darkened on exposure to light, decomposed at *ca.* 160°, and coupled with alkaline β-naphthol. When a solution of the above diazonium sulphate was stirred into glacial acetic acid (18 c.c.) at <20° and the mixture poured into iced water (300 c.c.), only slight precipitation occurred (0·05 g.).

*7-Nitro-*m*-nitrobenzenesulphon-2-naphthalide.* 7-Nitro-2-naphthylamine (6 g.) was intimately ground with *m*-nitrobenzenesulphonyl chloride (75 g.) and the mixture heated under reflux with pyridine (25 c.c.) for 3 hours. The solution was cooled to 0° and then stirred dropwise into 15% aqueous hydrochloric acid (200 c.c.); the precipitate of 7-nitro-*m*-nitrobenzenesulphon-2-naphthalide (9·1 g.) was filtered off, washed with water, sucked as dry as possible on the Büchner funnel, and crystallised twice from 70% acetic acid (charcoal). It was obtained in clusters of golden needles, m. p. 212—213° (Found: N, 11·4; S, 8·5. $C_{16}H_{11}O_6N_3S$ requires N, 11·2; S, 8·6%).

*The Nitration of 7-Nitro-*m*-nitrobenzenesulphon-2-naphthalide.*—(a) *With an equimolecular amount of nitric acid in glacial acetic acid.* The naphthalide (2 g.) was boiled with glacial acetic acid (15 c.c.), the mixture cooled to 50°, and a crystal of sodium nitrite added, followed by the dropwise addition, with stirring, of 2 c.c. of a solution of nitric acid (4·4 c.c.; *d* 1·5) in glacial acetic acid (35·6 c.c.). The temperature was then raised and kept at 80° for 5 minutes. 3 Hours later, glacial acetic acid (15 c.c.) was added at 15° with stirring, and next morning the suspension was filtered, and the solid 1 : *7-dinitro-*m*-nitrobenzenesulphon-2-naphthalide* (1·7 g.) washed with glacial acetic acid and ether, and dried; it crystallised from glacial acetic acid (charcoal), in which it is sparingly soluble, in yellow micro-needles, m. p. 246—247° (decomp.) (Found: N, 13·3. S, 7·8. $C_{16}H_{10}O_8N_4S$ requires N, 13·4; S, 7·7%).

(b) *With 5-fold excess of nitric acid in glacial acetic acid.* With the same procedure as above but with 10 c.c. of nitrating reagent, the yield of 1 : 7-dinitro-*m*-nitrobenzenesulphon-2-naphthalide was practically unchanged (1·8 g.; m. p. 246—247°). Hydrolysis occurred when the naphthalide (1 g.) was stirred into sulphuric acid (50 c.c.; *d* 1·84) and slow dissolution completed by heating to 70°. The clear solution was kept overnight; it was filtered on to ice, and the 1 : 7-dinitro-2-naphthylamine which precipitated was crystallised from glacial acetic acid (charcoal); it formed golden yellow needles, m. p. and mixed m. p. with an authentic specimen, 248—249°.

(c) *With nitric acid* (d 1·5). The powdered naphthalide (2·8 g.) was added portionwise during 15 minutes to nitric acid (15 c.c.; *d* 1·5), initially below 5°, and the temperature not allowed to exceed 20°; it was raised to 35° when complete dissolution had occurred. After 3 hours the solution was cooled to 0°, glacial acetic acid (15 c.c.) was added, and overnight 1 : 5(?) : *7-trinitro-*m*-nitrobenzenesulphon-2-naphthalide* separated in yellow micro-needles, m. p. 248° (decomp.); it recrystallised from glacial acetic acid in pale yellow, matted, silk-like needles, m. p. 262° (decomp.) (Found: N, 14·9; S, 7·27. $C_{16}H_9O_{10}N_5S$ requires N, 15·1; S, 6·9%). When this was hydrolysed, as described above for the dinitro-compound, 1 : 5(?) : *7-trinitro-2-naphthylamine* was obtained, which crystallised from glacial acetic acid (charcoal) in golden yellow needles, m. p. 291—292° (Found: N, 19·9. $C_{10}H_6O_6N_4$ requires N, 20·1%), which would not form a picrate. Attempts to deaminate this compound were unsuccessful.

The authors thank Imperial Chemical Industries Ltd. for a Research Scholarship and the Bradford Education Authority for the Harlow Research Fellowship to one of them (R. E. D.), and I.C.I. Ltd., Dyestuffs Division, for gifts of chemicals.

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164. *Some Derivatives of 5-Nitro-2-naphthylamine with a Note on its Preparation.*

By HERBERT H. HODGSON and RAYMOND E. DEAN.

From a review of existing methods, it would appear that the most serviceable method for the preparation of 5-nitro-2-naphthylamine is the reduction of 1 : 6-dinitronaphthalene by alkaline hydrosulphide. 5-Nitro-*m*-nitrobenzenesulphon-2-naphthalide is nitrated further only by excess of nitric acid (*d* 1·5) to give 1 : 5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide, a compound which monobrominates, probably to 3-bromo-1 : 5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide. The 2-bromo-5-nitronaphthalene now described completes the set of bromonitronaphthalenes.

OF the methods extant for the preparation of 5-nitro-2-naphthylamine, several involve the simultaneous production of the isomeric 8-nitro-2-naphthylamine. For example, the procedures described by Friedländer and Szymanski (*Ber.*, 1892, **25**, 2076), Morgan and Chazan (*J. Soc. Chem. Ind.*, 1922, **41**, 1T, 61T), and Morgan and Jones (*ibid.*, 1923, **42**, 341T) are based on the addition of β-naphthylamine nitrate to concentrated sulphuric acid at < −5°, with the subsequent tedious separation of the two bases by fractional crystallisation of their hydrochlorides, sulphates, or oxalates. The solubilities, however, of the free bases or their salts in various solvents are so similar, that separation is difficult. The proportions in which the isomerides occur are difficult to determine, since the diagram of the mixed m. p.s is indefinite over a wide range, but from the experimental fact that 5-nitro-2-naphthylamine is relatively much easier to obtain in greater yield and higher purity than the 8-nitro-isomeride, it would appear to preponderate in the mixture.

Hodgson and Crook's method (*J.*, 1936, 1844), which depends on the nitration of phthalo-β-naphthylimide, is superior from the manipulative point of view, since the higher temperature employed enables more rapid nitration, and a method of hydrolysis of the mixed phthalo-5- and -8-nitronaphthylimides by ethanol–hydrochloric acid (cf. Hey and Lawton, *J.*, 1940, 381) is now described, as an alternative to that by aqueous ammonia under pressure.

It is concluded that the most serviceable method for the preparation of pure 5-nitro-2-naphthylamine in good yield involves the deamination of 1 : 6-dinitro-2-naphthylamine (Hodgson and Turner, *J.*, 1943, 318), and the reduction of 6-nitro-group of the 1 : 6-nitronaphthalene by the aqueous sodium sulphide–sodium hydrogen carbonate–methanol procedure of Hodgson and Birtwell (*J.*, 1944, 75) (cf. also, improvements by Hodgson and Ward, *J.*, 1945, 590, 663, 794; 1948, 242).

The 2-bromo-5-nitronaphthalene, prepared from the 5-nitro-2-naphthylamine by the Sandmeyer reaction, together with the 1-bromo-7-nitronaphthalene (Hodgson and Dean, *J.*, 1950, 818) complete the set of bromonitronaphthalenes.

The further nitration of 5-nitro-*m*-nitrobenzenesulphon-2-naphthalide gives 1 : 5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide, independently of whether the calculated amount or an excess of nitric acid (*d* 1·5) is used, whereas (cf. p. 820) the action of excess of nitric acid (*d* 1·5) on 7-nitro-*m*-nitrobenzenesulphon-2-naphthalide is to give 1 : 5(?) : 7-trinitro-*m*-nitrobenzenesulphon-2-naphthalide.. The 1 : 5-dinitro-compound gives a monobromo-derivative to which the structure 3-bromo-1 : 5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide is assigned by analogy with the results of Consden and Kenyon (*J.*, 1935, 1595).

EXPERIMENTAL.

Acid Hydrolysis of the Mixture of Phthalo-5- and -8-nitro-2-naphthylimides.—The mixture (95 g.) was heated under reflux with ethanol (750 c.c.) and hydrochloric acid (225 c.c.; *d* 1·2) for 8 hours, a further quantity of hydrochloric acid (20 c.c.) being added at hourly intervals. At the end of this period, a considerable amount of an orange solid was undissolved; it was filtered off and again heated under reflux as before for 8 hours, but even then an appreciable amount still remained undissolved. The two filtrates were combined, cooled, and stirred into iced water, and the mixture of bases precipitated by ammonia (32 g.; m. p. 70—80°) and dried. Ethanol–sulphuric acid attacked the mixed phthalimides more rapidly, but side reactions led to a decreased yield of the mixed bases.

*5-Nitro-*m*-nitrobenzenesulphon-2-naphthalide.*—5-Nitro-2-naphthylamine (10 g.) and *m*-nitrobenzenesulphonyl chloride (15 g.) were intimately ground together in a mortar, the mixture heated under reflux for 3 hours with pyridine (30 c.c.), and the solution cooled to 0° and stirred into iced 15% hydrochloric acid (200 c.c.). The resulting *naphthalide* was dissolved in boiling 70% acetic acid (charcoal), and the filtered solution allowed to crystallise (16·2 g.; 81·6%); it recrystallised from hot glacial acetic acid in brown micro-crystals, m. p. 171° (Found: N, 11·4. $C_{16}H_{11}O_6N_3S$ requires N, 11·2%).

*Mononitration of 5-Nitro-*m*-nitrobenzenesulphon-2-naphthalide.*—The powdered compound (5 g.) was boiled with glacial acetic acid (25 c.c.), the temperature allowed to fall to 50°, and a crystal of sodium nitrite added followed by the dropwise addition with stirring of 2 c.c. of a solution of nitric acid (5·6 c.c.; *d* 1·5) in glacial acetic acid (14·4 c.c.); the temperature rose to 60°, after which it was raised to 75° for 5 minutes, and the mixture kept for 5 hours at room temperature. Glacial acetic acid (20 c.c.) was then added, and the precipitate (5 g.) filtered off, washed with glacial acetic acid and ether, and dried at 100°. The 1 : *5-dinitro-*m*-nitrobenzenesulphon-2-naphthalide* crystallised from glacial acetic acid in pale yellow needles, m. p. 216° (Found: N, 13·6. $C_{16}H_{10}O_8N_4S$ requires N, 13·4%). Excess of nitric acid (*d* 1·5) afforded the same product. This compound (1 g.) was hydrolysed by sulphuric acid (*d* 1·84) at 50° for 15 minutes and gave 1 : 5-dinitro-2-naphthylamine, which crystallised from glacial acetic acid in golden brown needles, m. p. 193° (Bell, *J.*, 1929, 2784, gives m. p. 191°), and, when diazotised by Hodgson and Walker's method (*J.*, 1933, 1620) and subsequently treated by the cuprous oxide–methanol procedure (cf. Hodgson and Turner, *J.*, 1942, 748; 1943, 86), it gave 1 : 5-dinitronaphthalene which crystallised from ethylene dichloride in yellow plates, m. p. and mixed m. p. with an authentic specimen, 216°.

Reaction of 1 : *5-Dinitro-*m*-nitrobenzenesulphon-2-naphthalide with Bromine.*—A solution of the naphthalide (5 g.) in pyridine (15 c.c.) was stirred and bromine (0·6 c.c.) added dropwise below 20°, the mixture kept overnight, then cooled to 5° and stirred into iced 15% hydrochloric acid (100 c.c.). The reddish-brown precipitate (5 g.) of 3-*bromo*-1 : *5-dinitro*-m-*nitrobenzenesulphon-2-naphthalide* was washed with water and dried at 100°; it crystallised from glacial acetic acid in golden-yellow micro-needles, m. p. 234° (Found: N, 11·5; Br, 16·0. $C_{16}H_9O_8N_4BrS$ requires N, 11·3; Br, 16·1%).

2-Bromo-5-nitronaphthalene.—A solution of 5-nitro-2-naphthylamine (2 g.) in sulphuric acid (5 c.c.; *d* 1·84) at 10° was stirred with one of sodium nitrite (1 g.) in sulphuric acid (5 c.c.; *d* 1·84) at <20°, and, when diazotisation was complete, the mixture was stirred into a solution of cuprous bromide (2·5 g.) in hydrobromic acid (25 c.c.; *d* 1·7). After reaction had ceased the mixture was poured into iced water, the precipitate of *2-bromo-5-nitronaphthalene* filtered off, washed with water, 2% aqueous sodium carbonate, and water, and dried at 40°. It crystallised from ethanol (charcoal) in light brown rods, m. p. 98—99° (Found: N, 5·6; Br, 31·6. $C_{10}H_8O_2NBr$ requires N, 5·5; Br, 31·7%).

The authors thank Imperial Chemical Industries Ltd. for a Research Scholarship and the Bradford Education Authority for the Harlow Fellowship to one of them (R. E. D.), and I.C.I. Ltd., Dyestuffs Division, for gifts of chemicals.

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165. *The Bromination of 6-Nitro-1-naphthylamine.*

By HERBERT H. HODGSON and RAYMOND E. DEAN.

6-Nitro-1-naphthylamine dibrominates in chloroform solution at −5° to give 2 : 4-dibromo-6-nitro-1-naphthylamine whatever the amount of bromine used. The monobromination previously reported by Hodgson and Turner (*J.*, 1943, 392) using the calculated amount of bromine is found to give a mixture of 2 : 4-dibromo-6-nitro-1-naphthylamine and unchanged 6-nitro-1-naphthylamine.

1-BROMO-7-NITRONAPHTHALENE has been prepared recently by the deamination of 1-bromo-7-nitro-2-naphthylamine (see p. 818), and is not identical with the specimen reported by Hodgson and Turner (*J.*, 1943, 392), which was obtained by the deamination of 4-bromo-6-nitro-1-naphthylamine, itself prepared by the apparent monobromination of 6-nitro-1-naphthylamine in chloroform with the calculated amount of bromine. Since it appeared unlikely that monobromination of 7-nitro-2-naphthylamine would occur in any than the 1-position, and therefore that the compound reported by Hodgson and Dean (*loc. cit.*) was 1-bromo-7-nitronaphthalene, the original bromination of 6-nitro-1-naphthylamine has been repeated. Under the conditions previously employed by Hodgson and Turner (*loc. cit.*), it was found that dibromination always occurred with formation of 2 : 4-dibromo-6-nitro-1-naphthylamine, even when only sufficient bromine was used to effect monobromination. This result is in line with the nitration of toluene-*p*-sulphon-1-naphthalide which always gives the dinitro-compound (Hodgson and Walker, *J.*, 1934, 180).

Repeated fractional crystallisation, with microscopic examination, of Hodgson and Turner's original specimen revealed it to be a mixture of unchanged 6-nitro-1-naphthylamine and its 2 : 4-dibromo-derivative, which would account for the analytical data obtained.

EXPERIMENTAL.

Preparation of 2 : 4-*Dibromo-6-nitro-1-naphthylamine.*—A solution of 6-nitro-1-naphthylamine (2·15 g., in chloroform (55 c.c.) was cooled to −5°, and bromine (1·3 c.c.) in chloroform (12 c.c.) was stirred in dropwise during ten minutes. The mixture was kept for 30 minutes at −5° with occasional stirring to ensure completion of the reaction, and the cream precipitate of 2 : 4-*dibromo-6-nitro-1-naphthylamine hydrobromide* (Found: Br, 56·0. $C_{10}H_7O_2N_2Br_3$ requires Br, 56·2%) filtered off and washed with chloroform and ether; it tended to hydrolyse in the air. The salt was basified with ammonia, the 2 : 4-dibromo-6-nitro-1-naphthylamine (2·3 g.) filtered off, washed with water, dried at 100°, and recrystallised twice from ethanol; it was obtained in red needles, m. p. 202° (Found: N, 8·5; Br, 46·0. Calc. for $C_{10}H_6O_2N_2Br_2$: N, 8·1; Br, 46·2%). In an attempt to obtain a monobromo-derivative, the above procedure was repeated with less bromine (0·25 c.c.), whereby a mixture of 2 : 4-dibromo-6-nitro-1-naphthylamine and 6-nitro-1-naphthylamine was obtained.

1 : 3-*Dibromo-7-nitronaphthalene.*—2 : 4-Dibromo-6-nitro-1-naphthylamine (2·1 g.) was dissolved in boiling glacial acetic acid (35 c.c.) and the solution rapidly chilled to 15° to obtain a fine suspension of the amine, which was then diazotised by addition to a stirred solution of sodium nitrite (1 g.) in sulphuric acid (20 c.c.; *d* 1·84) below 20°. After 30 minutes the solution of the diazonium sulphate was stirred into a hot suspension of cuprous oxide (4 g.) in methanol (70 c.c.), and the mixture was stirred for 1 hour and added to iced water (60 c.c.). Next morning the solid was filtered off, washed in the sequence water (300 c.c.), 2% aqueous sodium carbonate (300 c.c.), and water (300 c.c.), and then extracted with boiling ethanol. The extract was filtered, boiled with animal charcoal, and filtered again; the filtrate was allowed to evaporate. The 1 : 3-*dibromo-7-nitronaphthalene* (0·45 g.) crystallised from ethanol in pale yellow rods, m. p. 195° (Found: N, 4·59; Br, 48·0. $C_{10}H_5O_2NBr_2$ requires N, 4·23; Br, 48·3%), which were very sparingly soluble in cold and rather more soluble in hot ethanol.

1 : 2 : 4-*Tribromo-6-nitronaphthalene.*—A solution of the above amine (1·0 g.) in boiling hydrobromic acid (1·3 c.c.; *d* 1·7) and water (7·5 c.c.) was chilled to 0° to give a fine suspension of the hydrobromide) which was then diazotised at 0° with a solution of sodium nitrite (1 g.) in the minimum amount of water. After 30 minutes the filtered solution was stirred into one of cuprous bromide (2·0 g.) in hydrobromic acid (5 c.c.; *d* 1·7) at 60°, and, when the reaction had ceased, the mixture was poured into iced water and the yellow precipitate filtered off, washed in the sequence water (300 c.c.), 2% aqueous sodium carbonate (100 c.c.), and water (300 c.c.), dried at 70°, and dissolved in boiling ethanol (charcoal). This solution

was filtered and allowed to evaporate, whereupon the *tribromo*-compound separated in clusters of bright yellow needles (0·6 g.), m. p. 165° (Found : Br, 58·2. $C_{10}H_4O_2NBr_3$ requires Br, 58·5%).

The authors thank Imperial Chemical Industries Ltd. for a Research Scholarship and the Bradford Education Authority for the Harlow Research Fellowship to one of them (R. E. D.); they also thank I.C.I. Ltd., Dyestuffs Division, for gifts of chemicals.

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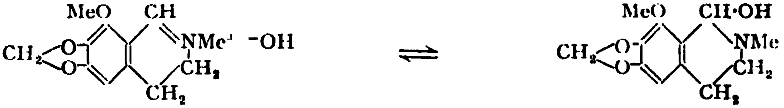
166. *The Isomerization of Berberine and Cotarnine Bases in Presence of Alkali.*

By BASIL SKINNER.

The action of potassium hydroxide on aqueous and alcoholic solutions of berberine and cotarnine hydrochlorides has been further investigated by the methods of absorption spectra and electrometric titration. The earlier work of Dobbie, suggesting that quaternary cotarninium hydroxide was converted into the ψ-base (cf. Hantzsch) in presence of excess of alkali hydroxide, is confirmed: the reaction is shown to be fast, and reversible by mineral acid; the concentration of alkali needed to effect the change is lower in alcoholic than in aqueous solution. Berberinium hydroxide behaves similarly, but is more stable in both solvents. Berberine base has been prepared in a strongly basic solid form, stable for some days. The various types of system covered by Hantzsch and Kalb's term ψ-base are discussed.

IN spite of the classical investigations by Hantzsch and by Dobbie, some uncertainty seems to exist about the relation of the ammonium and carbinol forms of berberine and cotarnine (cf. Henry, " Plant Alkaloids," 4th Edn., 1949, pp. 203, 333). Extending their observations with the aid of modern techniques, we have, in the main, confirmed their conclusions, although certain modifications have been found necessary.

The term ψ-ammonium base was coined by Hantzsch and Kalb (*Ber.*, 1899, **32**, 3109) to describe a quaternary base which became transformed, in certain conditions, into a feebly basic isomer, the ψ-base. The alkaloid cotarnine was cited as an example. Some of its properties pointed to formula (I), whilst others were best explained on the basis of (II) [cf., *e.g.*, Decker, *J. pr. Chem.*, 1893, [ii], **47**, 222; Day and Kantam, *J. Indian Chem. Soc.*, 1934, **11**, 835). Hantzsch and Kalb concluded that these two, and possibly other forms, existed in equilibrium, and that the free base isomerised instantly on treatment of the hydrochloride with silver oxide in aqueous suspension, since no drift in conductivity occurred on storage. In fact, however, the quaternary base was perfectly stable under these conditions, as is shown below.



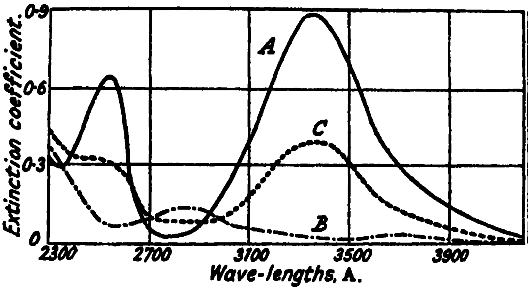
(I.) (II.)

Dobbie, Lauder, and Tinkler (*J.*, 1903, **83**, 598) investigated the problem further by means of absorption spectra. Cotarnine and its derivatives showed two types of spectrum: the first, with two well-marked absorption bands centred on 3278 and 2500 A., was shown by cotarnine and its hydrochloride in aqueous or alcoholic solutions. The second, showing less general absorption, with an ill-defined peak at 2857 A., was shown by solutions of cotarnine in non-hydroxylic solvents, by solutions of ψ-cotarnine cyanide in all solvents, and by aqueous solutions of cotarnine hydrochloride in presence of a large excess of 2N-sodium hydroxide; at lower concentrations of alkali, spectra intermediate between the two types were obtained. These authors associated the first type of spectrum with the ammonium form (I) and the second with the carbinol form (II): cotarnine and its salts formed the quaternary ion in hydroxylic solvents, except at high concentrations of alkali which favoured the carbinol form. In support of this, Freund, Hantzsch, and Kalb (*Ber.*, 1900, **33**, 380, 2201) showed that ψ-cotarnine cyanide had the structure (II; CN replaces OH).

As a preliminary step to a more quantitative investigation, we have determined more accurate absorption spectra and made further electrochemical measurements. The treatment was extended to berberine.

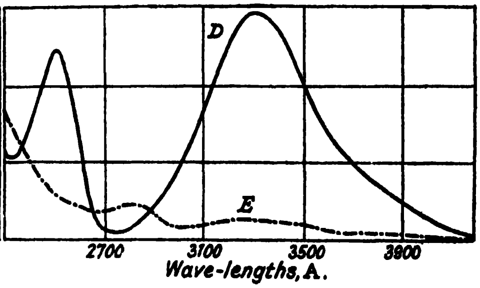
The absorption of alcoholic solutions of cotarnine hydrochloride is shown in Fig. 1, curve *A*. The positions of the absorption bands correspond fairly well with those of Dobbie *et al.* In aqueous solution (Fig. 2, curve *D*) the result is very similar. In alcoholic solution in presence of potassium hydroxide, the absorption is as in Fig. 1, curve *B*, at all alkali concentrations down to about 0·001N. At lower concentrations curves intermediate between *A* and *B* are obtained; *e.g.*, curve *C* of Fig. 1 was obtained in presence of $1·6 \times 10^{-4}$N-alkali and approximates to that expected from a mixture of 57% of form *A* and 43% of *B*. Although strict precautions to exclude carbon dioxide were taken up to the moment of filling the spectrophotometer cells, it was not possible to exclude it during the measurements, so that the alkali concentrations must be regarded as maxima rather than as precise.

FIG. 1.



Absorption spectra of: A, *cotarnine hydrochloride in ethanol;* B, *the same* + $7·8 \times 10^{-4}$N-KOH; C, *the same* + 0·25N-KOH.

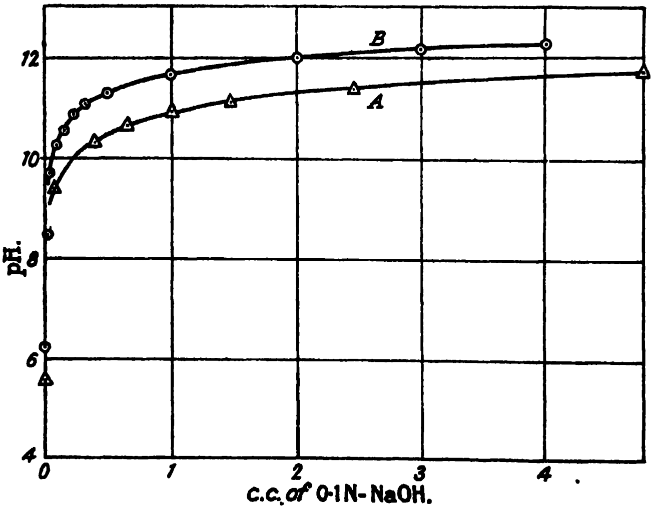
FIG. 2.



Absorption spectra of: D, *cotarnine hydrochloride in water;* E, *the same* + 0·25N-NaOH.

In aqueous solution, the effect of adding alkali is similar (Fig. 2, curve *E*); but a greater proportion of form *A* exists at equilibrium for a given concentration of alkali than in alcoholic solution, for curve *E*, obtained in presence of 0·25N-sodium hydroxide, appears to be made up of 90% of *B* and 10% of *A*. The initial concentration of cotarnine hydrochloride in all these experiments was 0·016 g. per l. ($5·48 \times 10^{-5}$M.). The transition from the yellow (*A*) to the colourless form appeared to be almost instantaneous, and was immediately reversed by the addition of a slight excess of dilute hydrochloric acid.

FIG. 3.



Titration of (A) *cotarnine hydrochloride and* (B) *berberine hydrochloride.*

A few electrometric experiments were carried out. First a 0·0104N-solution of cotarnine hydrochloride in water was titrated with 0·106N-sodium hydroxide. The changes in pH during titration are shown in Fig. 3: cotarnine behaves as a typical strong base, no buffering action being evident.

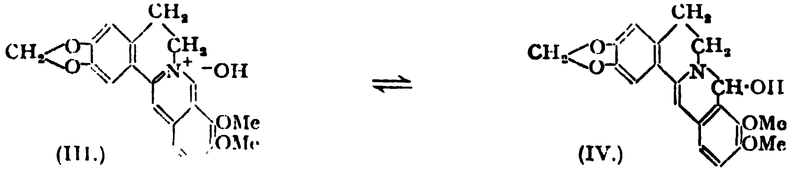
The specific conductivity of the same cotarnine hydrochloride solution at 25° was 0·00263.

On addition of 2·5 c.c. of the sodium hydroxide solution to 25 c.c. of the hydrochloride solution so as approximately to neutralise the latter, the conductivity rose to 0·00694, as would be expected of a strong base. After four days the conductivity was 0·00685, indicating the high stability of the quaternary base; this was confirmed by half-neutralising the cotarnine hydrochloride solution with sodium hydroxide and measuring the pH value, which was found to be 11·40; after storage for twelve days in presence of soda-lime, the pH had fallen only to 11·20.

Attempts to prepare the ammonium form of cotarnine in the solid state were unsuccessful owing to decomposition.

The earlier conclusions of Dobbie, Lauder, and Tinkler are thus well borne out. A solution of cotarnine base, in absence of excess of alkali, is stable for days in aqueous solution as the quaternary ion (Form *A*). Addition of alkali causes conversion into the colourless feebly basic isomer to which the carbinol structure is usually assigned, the change being reversed on the addition of acid. This change is brought about very much more easily in alcoholic than in aqueous solution, since the more polar solvent water naturally favours the stability of the quaternary ionic form with its high solvation energy.

The alkaloid berberine present similar difficulties. Gadamer (*Arch. Pharm.*, 1901, **239**, 648) found that addition of aqueous barium hydroxide to berberine sulphate solution and filtration gave a reddish-brown, strongly alkaline solution which he supposed to contain the quaternary base, berberinium hydroxide (III). This strongly basic form existed, according to Gadamer, only in solution.


(III.) (IV.)

When the solution was treated with an excess of sodium hydroxide, a new ether-soluble form was obtained which gave an oxime; Gadamer called it berberinal, and gave it an aldehyde formula. Tinkler (*J.*, 1911, **99**, 1340) found that the absorption spectrum of berberine hydrochloride in alcoholic solution underwent, on addition of a small quantity of potassium hydroxide, a change similar to that occurring with cotarnine salts. The normal form possessed absorption peaks at 2275 and 2875 A., but in presence of alkali there was one broad absorption band, centred on 2700 A. The latter type of absorption resembled that of α-methyldihydroberberine, which according to Freund and Beck (*Ber.*, 1904, **37**, 4677) had a carbinol structure. Tinkler attributed the new spectrum to the conversion of the berberinium ion (I) into the carbinol (II) which he called berberinol and which was identical with the ether-soluble form.

In the present work the absorption spectrum of alcoholic or aqueous berberine hydrochloride ($3{\cdot}9 \times 10^{-5}$M.) was found to be as in Fig. 4, curve *A*. In aqueous solution, the addition of sodium hydroxide to a final concentration of 0·25N. had no effect. Very high concentrations of alkali gave a pale pink precipitate, rapidly becoming orange, which may be explained on the basis of Gadamer's observation (*loc. cit.*) that the ether-soluble form of berberine undergoes disproportionation to dihydroberberine and oxyberberine. Slow addition of 2N-sodium hydroxide to a 2×10^{-3}M-solution of the hydrochloride gave a water-soluble yellow precipitate, having the same absorption as the hydrochloride and composed mainly of berberine hydrochloride, salted out of solution.

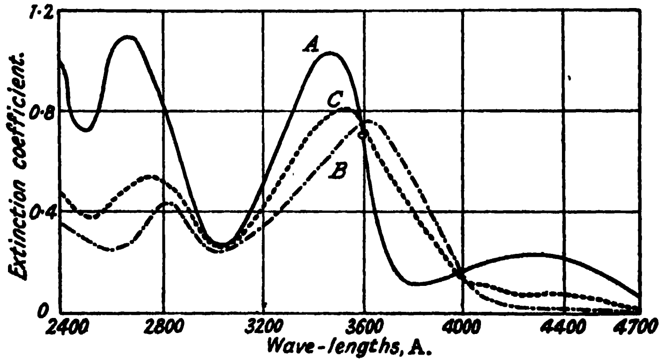
In alcoholic solution, very low concentrations of alkali change the form of the absorption curve *B* of Fig. 4, being obtained in all cases when the alkali is 2×10^{-3}N. or stronger. Curve *C* ($7{\cdot}8 \times 10^{-4}$N-KOH) corresponds approximately to that of a mixture of 25% of form *A* and 75% of *B*. The change was again instantaneous and reversed by the addition of acid.

These curves differ considerably from those obtained by Tinkler, who found that alcoholic berberinium chloride solutions show continuously increasing absorption from 3400 to 4500 A. (contrast curve *A* of Fig. 4) and that, even after the addition of potassium hydroxide, absorption was high between 3850 and 4500 A. Further, the wave-lengths of the maxima recorded by Tinkler are not in accord with the present work. More recently determined spectra of berberinium iodide (Feist, Awe, and Etzrodt, *Arch. Pharm.*, 1934, **272**, 820), and of an aqueous solution of berberine base (Chatterjee, *J. Indian Chem. Soc.*, 1942, **19**, 234) resemble Fig. 4, curve *A*, very closely, but no curves intermediate between the two extremes have previously been published. If berberine hydrochloride solution is shaken with silver oxide and filtered, the strongly alkaline solution gives the same spectrum as a solution of the hydrochloride (curve *A*) which must therefore be attributed to the quaternary berberinium ion (in accord with Tinkler's suggestion). Curve *B* likewise represents the spectrum of berberinol, while curve *C* is that of a mixture of the two substances.

The electrochemical measurements again bear out these conclusions. A 0·004M-solution of berberine hydrochloride, titrated against 0·110N-sodium hydroxide, yielded the curve shown in Fig. 3, which is again that of a typical strong base. The specific conductivity of the same berberine hydrochloride solution at 25° was 0·00111, rising to 0·00345 when 25 c.c. of the solution were nearly neutralised with 4·0 c.c. of the sodium hydroxide solution. This value was unchanged after four days. When the berberinium chloride solution was approximately half-neutralised, the pH was 11·70 and after four days (in presence of soda-lime) was still 11·60, again demonstrating the stability of the strong base. It was in this case possible to isolate the strong base in the solid state by the procedure which failed in the case of cotarnine (cf. p. 827).

Berberine and cotarnine both show, therefore, the same type of isomerism. They differ in the relative stabilities of the ammonium forms to alkali, berberine being more stable in both aqueous and alcoholic solution. It is hoped later to investigate more fully the nature of the common forms of solid cotarnine and berberine bases, and to study quantitatively the equilibrium :

FIG. 4.



Absorption spectra of : A, *berberine hydrochloride in alcohol ;* B, *the same* + $7·8 \times 10^{-4}$N-KOH; C, *the same* + 0·25N-KOH.

$$\mathrm{R{\cdot}CH{=}\overset{+}{N}{=}R' + \overset{-}{OH} \rightleftharpoons R{\cdot}CH(OH){-}N{=}R'} \quad . \; . \; . \; . \; . \; . \; . \quad (A)$$

for each alkaloid. From the figures quoted above, approximate values of the equilibrium constant of this reaction can be calculated to be : cotarnine (aqueous solution) 36, (alcoholic solution) $4·7 \times 10^3$; and berberine (alcoholic solution) $3·8 \times 10^3$. In view of the possible effect of carbon dioxide on the equilibria, and of the tentative nature of the above equation, confirmation of these values is necessary, although preliminary experiments indicate that the berberine equilibrium in alcoholic solution conforms to the mass law.

The term ψ-base, as used by Hantzsch and Kalb, covers two apparently different types of isomerism : first, where the quaternary base is stable in aqueous solution, but is changed rapidly into the feebly basic isomer on addition of alkali, and, secondly, where the quaternary base decomposes spontaneously on storage, in absence of excess of alkali. Cotarnine, which these authors believed to belong to the second class, is actually an example of the first. The difference is probably more apparent than real; for when the equilibrium constant of the reaction (*A*) is large, adding alkali to a solution of the hydrochloride of the base may give a hydroxyl-ion concentration sufficiently great to promote the isomerisation before neutralisation is complete. If the constant is small, an excess of alkali will be needed to bring about the change, so that the free base will be stable indefinitely in aqueous solution.

EXPERIMENTAL.

Physical Measurements.—Absorption spectra were measured at intervals of 50 A. by means of the Beckman spectrophotometer at room temperature (*ca.* 15°). The slit width was 1 mm. for the range of wave-lengths over which the hydrogen arc was employed (2200—3650 A.) and 0·1 mm. for wave-lengths above 3650 A. It was sometimes necessary to open the slit beyond 1 mm. for the shortest wave-lengths (2200—2400 A.) in order to obtain a balance with the instrument. The cells were of silica, 1 cm. thick, fitted with loose glass covers.

Measurements of pH were made with a Cambridge pH-meter (bench model) and a glass electrode, at 15°. The response of the glass electrode, which was calibrated against potassium hydrogen phthalate buffers, was slightly irregular at pH values above 10·5, giving high results.

Conductivity measurements were carried out by means of a Wheatstone network circuit with a 1000-cycle Mullard oscillator as current source. The cells were of glass, had a capacity of 25 c.c., closely fitting stoppers, and bright platinum electrodes, and were maintained at 25° by a thermostat. The conductivity water had a conductivity of less than 2×10^{-6}.

Materials.—The berberine hydrochloride was recrystallised twice from water containing a small quantity of hydrochloric acid, and washed twice with cold water before being dried. The cotarnine hydrochloride, obtained from a small pure sample was not recrystallised, but the absorption spectrum confirmed the purity. The aqueous sodium hydroxide used in the titrations was prepared immediately before use by diluting a saturated solution, in order to eliminate carbonate. Absolute alcohol was used throughout, and was redistilled, the first fraction being rejected, for the experiments involving low concentrations of potassium hydroxide, in order to eliminate carbon dioxide.

Berberinium Hydroxide.—0·004M-Berberine hydrochloride (25 c.c.) was shaken with moist silver oxide and filtered. The resulting solution was kept in a desiccator containing calcium chloride and sodium hydroxide for 24 days. The dark brown, hygroscopic residue was treated with 25 c.c. of water, in which it readily dissolved, apart from less than 5% of insoluble matter. The pH of the solution was 11·20 and, on dilution, the liquid had the typical absorption of berberine salts (Fig. 4, curve *A*). It is thus clear that, apart from the small proportion which yielded the insoluble matter, the berberinium hydroxide remained stable in the solid state.

Attempts to Prepare Cotarninium Hydroxide.—Shaking 0·0104N-cotarnine hydrochloride solution with silver oxide and filtration gave a solution (pH 11·50) which decomposed during evaporation on a water-bath. The residual solid was only partly soluble in water and had an odour of volatile amines. Addition of water to give the original volume yielded a solution of pH only 9·2. Decomposition, probably caused by oxidation, also occurred on evaporation of the solution for 24 days in a desiccator containing calcium chloride and sodium hydroxide.

The author thanks Professor R. D. Haworth, F.R.S., and Dr. J. C. Speakman for advice.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, September 29th,* 1949.]

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167. *Fucoidin. Part II. The Hydrolysis of a Methylated Fucoidin prepared from* Fucus vesiculosus.

By J. CONCHIE and E. G. V. PERCIVAL.

L-Fucose (*ca.* 1 part), 3-methyl L-fucose (*ca.* 3 parts) and 2 : 3-*dimethyl* L-*fucose* (*ca.* 1 part) have been identified in the carbohydrate portion of the hydrolysate of a methylated fucoidin. A branched structure in which 1 : 2-α-links predominate is suggested for the polysaccharide.

THE fucoidin used in this series of experiments was prepared from dried, ground *Fucus vesiculosus* collected in the summer months of 1945. The product was comparable with the specimens of fucoidin described in Part I (*J.*, 1950, 717) but the intensive purification was not applied. It had $[\alpha]_D^{15}$ −118°, gave 38% of L-fucose on hydrolysis, and contained Ca 5·9, Mg 0·2, Na 0·9, K 0·1—0·2, and SO_4 32·8%, the sulphate of the ash accounting for half the total sulphate. It required 36 hours at 100° to remove 36% of the total sulphate with N-sodium hydroxide.

Methylation with sodium hydroxide and methyl sulphate gave a product having $[\alpha]_D^{15}$ −107° and containing Ca 5·1, Mg 0·2, Na 0·8, K 0·05, SO_4 25·9, and OMe 15·8%, in which the sulphate in the ash comprised 57% of the total. Evidently, therefore, as for the carragheen polysaccharides (Buchanan, Percival, and Percival, *J.*, 1943, 51; Dewar and Percival, *J.*, 1947, 1622) the metals combined with the sulphate group were not displaced by sodium during the methylation process. That all the available hydroxyl groups were substituted in the above product was shown by the fact that on treatment with acetic anhydride and pyridine an insignificant amount of acetylation occurred. The acetyl content of fucoidin acetate was found to be 18·0%. If the basic formula is assumed to be $(C_6H_9O_3SO_4Ca_{0.5})_n$ the methylated derivative would contain OMe 12·0%, and the acetate OAc 15·0%. The slightly higher values obtained in practice are attributed to the presence of small amounts of more highly substituted " foreign " polysaccharides rather than to the loss of sulphate groups from the substituted fucose units during methylation.

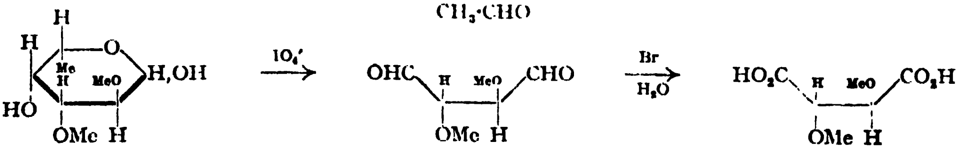
The methylated fucoidin was hydrolysed, and the products were converted into methylglycosides and separated by solvent extraction (Brown and Jones, *J.*, 1947, 1344) and on an alumina column. The only compounds to be isolated in quantity were methyl L-fucosides, and the following were found present: methyl-L-fucosides (*ca.* 20%), 3-methyl L-fucosides (*ca.* 57%), and 2 : 3-dimethyl L-fucosides (*ca.* 20%).

The monomethyl sugar was shown to be a derivative of L-fucose by conversion into 2 : 3 : 4-trimethyl α-methyl-L-fucoside. The methyl group was assigned to $C_{(3)}$ for the following reasons. Oxidation gave a lactone, m. p. 136°, $[\alpha]_D$ + 25° $\longrightarrow$ +75° (in water; 62 hours), with constants comparable with those of 3-methyl D-fuconolactone (digitalonolactone), m. p. 136—140°, [α] −22° $\longrightarrow$ −70° (60 hours), a specimen of which was prepared from digitalose isolated from *iso*emicymarin. The derived *amide* gave a positive Weerman test.

Further support for the view that we were dealing with 3-methyl L-fucose was derived from a direct comparison on the paper chromatogram with 2-methyl L-fucose, synthesised by the method of McPhillamy and Elderfield (*J. Org. Chem.*, 1939, **4**, 150), and with digitalose (3-methyl D-fucose). There was a distinct separation between 2-methyl L-fucose (R_G 0·56) (Hirst, Hough, and Jones, *J.*, 1949, 928) and digitalose (R_G 0·45), and the material under test was indistinguishable from the latter on the chromatogram. A small quantity of a monomethyl α-methyl-L-fucoside, m. p. 130—132°, $[\alpha]_D$ −173°, which was isolated on one occasion gave on hydrolysis a sugar chromatographically identical with digitalose and must therefore be designated *3-methyl α-methyl-L-fucoside.*

The dimethyl methylglycoside was shown to be a L-fucopyranose derivative by complete methylation to give trimethyl α-methyl-L-fucopyranoside. The methyl groups were assigned to $C_{(2)}$ and $C_{(3)}$ for the following reasons. Oxidation of the dimethyl sugar gave a syrupy lactone, $[\alpha]_D$ +9° $\longrightarrow$ +47° (22 hours), which was undoubtedly a furanolactone on account of its positive rotation [cf. 2 : 3 : 4-trimethyl L-fuconolactone, $[\alpha]_D$ −138° $\longrightarrow$ −36° (James and Smith, *J.*, 1945, 746)], thus excluding substitution on $C_{(4)}$. Synthetic 3 : 4-dimethyl L-fucose (Percival and Percival, *J.*, 1950, 690) failed to cause crystallisation on nucleation and 3 : 4-dimethyl α-methyl-L-fucoside had constants markedly different from the crystalline dimethyl methyl-L-fucoside, isolated from the dimethyl fraction in these experiments, which had m. p. 49—51° and $[\alpha]_D$ −190° and is designated 2 : *3-dimethyl α-methyl-L-fucoside.*

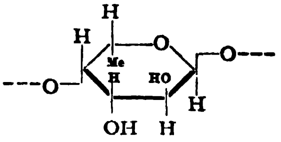
Direct chromatographic comparison with 3 : 4-dimethyl L-fucose (R_G 0·67—0·68) showed that although the rate of travel of the dimethyl fucose in question was closely similar (R_G 0·65), by running the paper strips for 48 hours with butanol–ethanol as solvent, the spots developed on spraying with aniline oxalate were distinctly differentiated. Evidence that a methoxyl group was present on $C_{(2)}$ was also given by the fact that the crystalline *dimethyl fuconamide* gave a negative Weerman test, and oxidation of the free sugar with periodate, followed by bromine water, esterification, and amide formation gave D(−)-dimethoxysuccinamide. This product could only arise if methoxyl groups were present on $C_{(2)}$ and $C_{(3)}$: as in

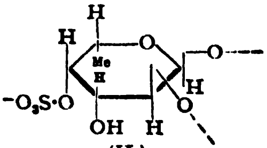


It was only the low yield of amide, attributed to the difficulties which occasionally arise on the oxidation of certain methylated sugars with periodate, which prevented this experiment from being quite conclusive; if the other evidence outlined above is also considered, there seems no reasonable doubt that the dimethyl sugar was, in fact, 2 : 3-dimethyl fucose.

In connection with the above work on partly methylated fucoses, attention should be drawn to the virtual failure of the periodate oxidation method as a test for the presence of a free hydroxyl group on $C_{(4)}$ in partly methylated 6-deoxyhexoses. The method for estimating fucose by periodate oxidation and conversion into acetaldehyde (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456; Cameron, Ross, and Percival, *J. Soc. Chem. Ind.*, 1948, **67**, 161) was applied to the monomethyl fucose (3-methyl fucose) and the dimethyl fucose (2 : 3-dimethyl fucose). Only one-third of the theoretical yield of acetaldehyde was obtained in each case, although this is much greater than the yield (5%) from 2 : 3-dimethyl rhamnose (Percival and Percival, *loc. cit.*). These results recall similar difficulties with partly methylated hexoses, for Jeanloz (*Helv. Chim. Acta*, 1944, **27**, 1509) and Bell, Palmer, and Johns (*J.*, 1948, 992) showed that in the oxidation of methylated sugars such as 2 : 3 : 4-trimethyl glucose, 2 : 4-dimethyl galactose, and 3-methyl glucose by periodate in buffered solutions, the yield of formaldehyde was much lower than the theoretical.

Before an attempt is made to draw a preliminary picture of the possible structure of fucoidin, one important fact should be noted. Since the sulphate groups are stable to alkali (apart from the fairly rapid initial removal of *ca.* 10% of the total sulphate which will require further study), it is clear that the main linkage of L-fucopyranose units cannot be through the hydroxyl group on $C_{(4)}$ as the hydroxyl groups on $C_{(3)}$ and $C_{(3)}$ are *trans* to one another (I). A sulphate


(I.)

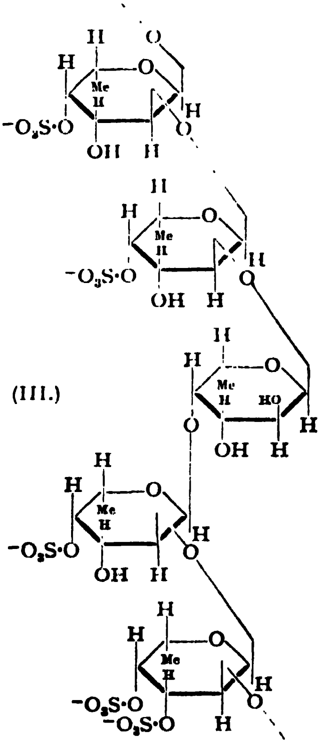

(II.)

group in either of these positions would be readily eliminated by alkali (Percival, *Quart. Rev.*, 1949, **3**, 369). The isolation of 3-methyl L-fucose leaves only one possible arrangement (II) for those residues carrying one free hydroxyl group, namely a 1 : 2-linkage with the sulphate on $C_{(4)}$. Because of the strongly negative rotations of fucoidin and its derivatives, these junctions are considered to be predominantly of the α-type.

There are two possible ways of accounting for the free fucose residues in methylated fucoidin, excluding the possibility of incomplete methylation owing to steric effects. First, some fucose residues might carry two sulphate groups, a possibility by no means out of the question since the proportion of sulphate to fucose in the original fucoidin is somewhat higher than is demanded by a 1 : 1. ratio, although contamination with a galactan sulphate would also explain this. The 2 : 3-dimethyl fucose could be explained by the appearance of occasional 1 : 4-linkages, and these residues would require to be unsubstituted by sulphate groups (cf. III).

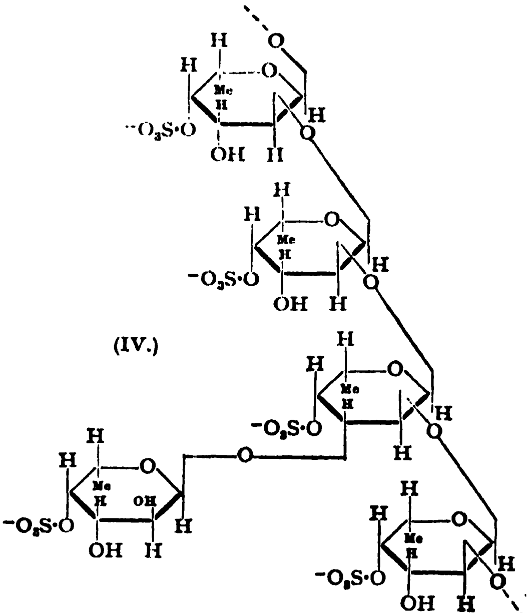
If the conclusions as to the main structural feature are correct, the 2 : 3-dimethyl fucose could not arise as a result of the loss of sulphate groups during methylation since this would produce the 3 : 4-isomer.

(III.)



$$\begin{array}{ccccc} & & & & SO_4^- \\ & & & & 3 \\ ---1F2, & 1F2, & 1F4, & 1F2, & 1F2--- \\ 4 & 4 & & 4 & 4 \\ SO_4^- & SO_4^- & & SO_4^- & SO_4^- \end{array}$$

(IV.)



$$\begin{array}{cccc} & F4SO_4^- & & \\ & 1 & & \\ & 3 & & \\ ---1F2, & 1F2, & 1F2, & 1F2--- \\ 4 & 4 & 4 & 4 \\ SO_4^- & SO_4^- & SO_4^- & SO_4^- \end{array}$$

F = L-Fucopyranose.

Another possible explanation is that the free fucose originates from branching points carrying terminal groups having free hydroxyls on $C_{(2)}$ and $C_{(3)}$. From the proportions of the various sugars isolated there would be an average of one such branch in every five fucose units (cf. IV).

For either of the two possibilities it will be observed that one equivalent of periodate would be consumed for each unit of five fucose residues. Because of the presence of impurities, this figure cannot be determined with any accuracy at present, but, if the galactose, xylose, and uronic acid known to be present are assumed to be linked by 1 : 4-linkages and a correction is made for the consumption of periodate by these materials, fucoidin reacts with M/10-sodium periodate in 24 hours so that one equivalent of periodate is accounted for by 880 g. of the " ideal " polysaccharide, which corresponds to between three and four monosaccharide units.

Before anything approaching the last word on the constitution of fucoidin can be written, it will be necessary to study more highly purified specimens, and preparations from different algae. Progress will undoubtedly be slow for technical reasons, but this preliminary study may stimulate other workers to attack this problem, which has added interest owing to the discovery by Vasseur (*Acta Chim. Scand.*, 1948, **2**, 900) of fucosan sulphates in the jelly coat of sea-urchin eggs of the species *Strongylocentrus droebachiensis, Echinocardium cordatum,* and *Paracentrotus lividus.*

EXPERIMENTAL.

Preparation of the Polysaccharide.—The polysaccharide was extracted as described in Part I (*loc. cit.*). For this investigation specimens of *Fucus vesiculosus* (May, June, July, 1945 samples) kindly supplied by The Scottish Seaweed Research Association, Musselburgh, were used. Purification was effected by allowing a solution of the polysaccharide in water to stand over " Filter-Cel " for several days, followed by filtration, concentration, and pouring into alcohol. The process was repeated till a constant fucose content was obtained. The resulting white fibrous product had $[\alpha]_D^{15}$ $-118°$. For all quantitative work the polysaccharide was dried over phosphoric oxide at 50°/15 mm. to constant weight [Found : ash (as sulphate), 24·1 ; Ca, 5·9 ; Na, 0·9 ; Mg, 0·2 ; K, 0·1 – 0·2 ; SO_4 (total), 32·8% ; SO_4 (in ash), 17·6%]. Estimation of fucose by periodic acid oxidation (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456 ; Cameron, Ross, and Percival, *J. Soc. Chem. Ind.*, 1948, **67**, 161) gave 37·8% of fucose.

Hydrolysis of Fucoidin with N*-Sodium Hydroxide at* 100°.—The polysaccharide (1·1082 g.) was heated with N-sodium hydroxide (200 c.c.) at 100° in the presence of barium chloride (1·283 g.). At definite intervals, samples (15 c.c.) were withdrawn, water (15 c.c.) and dilute acetic acid (5 c.c.) were added, and the solution was centrifuged. The residual combined sulphate in 50 c.c. of the solution was then determined by hydrolysis with hydrochloric acid and weighing of the barium sulphate produced :

Time (hrs.)	0	½	1	4	10	20	30	36	48	56	72
Residual sulphate ($BaSO_4$, mg.)	48·5	45·6	43·0	41·2	38·9	38·2	32·0	30·9	25·1	24·1	20·0
Hydrolysis, %	0	6·0	11·4	15·0	19·8	26·1	34·1	36·4	48·2	50·3	58·7

Acetylation of Fucoidin.—The polysaccharide (2 g.) was dissolved in distilled water (30 c.c.), pyridine (120 c.c.) was added, and the pyridine–water azeotrope distilled off at 50°/15 mm (Pacsu and Mullen, *J. Amer. Chem. Soc.*, 1941, **63**, 1487). The distillation was continued till the volume of residual solution was *ca.* 30 c.c., a brown gelatinous mass being obtained. Pyridine was added to bring the volume to 50 c.c., followed by acetic anhydride (25 c.c.) added slowly, with shaking and cooling. After being left in the dark (2 days) the acetate was separated at the centrifuge, washed with pyridine, alcohol, and ether, and dried, to give a white powder (2 g.) [Found : $CH_3{\cdot}CO$, 18·0. Calc. for $C_6H_8O_7(CO{\cdot}CH_3)SCa_{0.5}$: $CH_3{\cdot}CO$, 15·0%).

Typical Methylation.—Deacetylation and methylation proving no more satisfactory than direct methylation, the direct method was used throughout the investigation.

The polysaccharide (10 g.), dissolved in the minimum of water, was treated with methyl sulphate (240 c.c.) and sodium hydroxide (672 c.c. ; 30%) in one-eighth portions every 2 minutes, followed by methyl sulphate (120 c.c.) and sodium hydroxide (208 c.c. : 30%) in one-eighth portions every 10 minutes, the solution being stirred and the temperature kept at 50° during the methylation. The solution was then heated to 85° for 30 minutes, cooled, neutralised with glacial acetic acid, and dialysed against running water till sulphate-free (10 days). On evaporation at 45°/15 mm. a brown glass was obtained (Found : OMe, 7·2%). This glass was taken up in water and the methylation procedure repeated 3 times, after which the methoxyl content remained unchanged on further methylation (Found : OMe, 15·8%); yield, 6·8 g.

To ascertain whether or not the polysaccharide was fully methylated, it was acetylated as described above. Examination of the product obtained (Found : CH_3CO, $<1\%$) appeared to indicate, within experimental error, that the polysaccharide was fully methylated. The product, after drying over phosphoric oxide at 50°/15 mm., had $[\alpha]_D^{15}$ $-107°$ (*c*, 1·0 in water) [Found : ash (as sulphate) 21·2 ; Ca, 5·1 ; Na, 0·8 ; Mg, 0·2 ; K, 0·05 ; SO_4 (total), 25·9 ; SO_4 (in ash), 14·8%].

Hydrolysis of the Methylated Polysaccharide.—The above product (5·01 g.) was hydrolysed at 100° with oxalic acid (200 c.c. ; 3%) to constant rotation. The solution was neutralised with barium carbonate and worked up in the usual way to give a yellow syrup (3·3 g.), $[\alpha]_D^{15}$ $-54·0°$ (*c* 1·0 in water) (Found : OMe, 20·4%). Estimation of fucose by periodic acid oxidation (Cameron, Ross, and Percival, *loc. cit.*) gave 30·4% as the apparent fucose content or 33·0% calculated as monomethyl fucose.

Glycopyranoside Formation.—The hydrolysed methylated polysaccharide (8·9 g.) was boiled with methanolic hydrogen chloride (400 c.c. : 2%) until non-reducing (5 hours), neutralised with silver carbonate, evaporated, and extracted with alcohol, to give on evaporation a yellow syrup (5·8 g.). Fractionation by distillation in a high vacuum was unsuccessful, but one fraction (b. p. 125—150°/0·1 mm.; n_D^{11} 1·4717; OMe, 29·8%) gave, on hydrolysis and osazone formation, a small yield of an osazone, m. p. 178—179° (decomp.) (Found: OMe, 9·2. Calc. for $C_{19}H_{24}O_3N_4$: OMe, 8·7%), which was presumed to be 3-methyl phenylfucosazone.

Fractionation by Chromatographic Adsorption on Alumina.—The glycosides were dissolved in chloroform–light petroleum (1 : 1) and introduced into a column (30 × 2 cm.) of activated alumina (Spence and Sons: Grade H) suspended in the same solvent. The column was developed first with the same mixture, then with increasing proportions of chloroform, followed by mixtures of chloroform and methanol, and finally pure methanol. Six fractions were obtained: (1) 1·036 g., n_D^{13} 1·4590, (2) 0·124 g. (partly crystalline), n_D^{12} 1·4580, (3) 1·680 g. (partly crystalline), n_D^{12} 1·4670, (4) 1·192 g., n_D^{12} 1·4688, (5) 0·878 g., and (6) 0·182 g. Recovery was 88%.

Examination of fraction (1). This fraction (0·97 g.) on distillation gave fractions (1*a*) 0·478 g., b. p 75—80°/0·03 mm., n_D^{13} 1·4549 (Found: OMe, 46·6%), and (1*b*) 0·385 g., b. p. 90—110°/0·03 mm.; n_D^{13} 1·4601 [Found: OMe, 47·7. Calc. for $C_6H_9O_2(OCH_3)_3$: OMe, 45·1%]. Later experiments using the paper chromatogram showed the two fractions to be identical.

Formation of 2 : 3 : 4-*trimethyl* α-*methyl*-L-*fucoside from fraction* 1a. This fraction (0·2 g.), after two treatments with Purdie's reagents, gave white needles (0·18 g.), m. p. 84—89°, subliming *in vacuo*, $[\alpha]_D^{14}$ −192° (*c*, 1·08) [Found: OMe, 56·1. Calc. for $C_{10}H_{20}O_5$: OMe, 56·3%]. A mixed m. p. determination with authentic 2 : 3 : 4-trimethyl α-methyl-L-fucoside showed no depression.

Periodic acid oxidation of fraction 1b. *Isolation of* D(−)-*dimethoxysuccinamide*. The syrup (0·2 g.) was hydrolysed with sulphuric acid (50 c.c.; 0·1N.) for 8 hours at 100° ($[\alpha]_D$ $-61° \longrightarrow -1°$) and the solution worked up in the usual manner. To the syrup so obtained was added periodic acid (20 c.c.: 0·5M.), and the solution was set aside for 20 hours at room temperature. After thorough aeration to remove the acetaldehyde, barium chloride (1·22 g.) was added to the solution, followed by barium carbonate in excess. The residue, after filtration, was extracted with a small quantity of water, and the extract added to the filtrate. Oxidation with bromine (3 c.c.) gave a small quantity of syrup which was boiled with methanolic hydrogen chloride (50 c.c.; 2·5%) for 5 hours and worked up in the usual way. Treatment of the resulting syrup with methanolic ammonia (2 c.c.) for 3 days at 0° gave a crystalline solid mixed with syrup. The long needle-shaped crystals (12 mg.) were washed with alcohol and dried, and then had m. p. 262—263° and $[\alpha]_D^{15}$ −92° (*c*, 2·01 in water) (Found: OMe, 34·8. Calc. for $C_6H_{12}O_4N_2$: OMe, 35·3%). A mixed m. p. determination with authentic D(−)-dimethoxysuccinamide, m. p. 265—268°, $[\alpha]_D$ −94°, showed no depression, but one with (±)-dimethoxysuccinamide showed a large depression.

Examination of crystalline portion of fraction 2. 2 : 3-*Dimethyl* α-*methyl*-L-*fucoside*. After fraction 2 had been dried on a tile and recrystallised from light petroleum (b. p. 40—60°) a small quantity of crystals (12 mg.) was obtained, having m. p. 49—51°, $[\alpha]_D^{15}$ −190° (*c*, 1·4 in water) (Found: C, 52·3; H, 8·6; OMe, 44·3. $C_9H_{18}O_5$ requires C, 52·4; H, 8·7; OMe, 45·1%).

Examination of fraction 3. *Isolation of* 3-*methyl* α-*methyl*-L-*fucoside*. This fraction was partly crystalline, and an attempt was made to obtain a greater yield of crystals by fractionation using a column of alumina and developing with chloroform–methanol (3 : 1). The crystalline fraction so obtained was dried on a porous tile and recrystallised from ethyl acetate, and then had m. p. 130—132°, $[\alpha]_D^{14}$ −173° (*c*, 0·4 in water) (Found: C, 50·3; H, 8·4; OMe, 32·1. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3; OMe, 32·3%).

Hydrolysis with sulphuric acid (0·1N.) for 8 hours gave the free sugar as a syrup, $[\alpha]_D^{15}$ −94° (c, 0·51) Found: OMe, 17·8. $C_7H_{14}O_5$ requires OMe, 17·4%). This sugar was compared on the same paper) chromatogram with synthetic 2-methyl L-fucose (R_G 0·56) and digitalose (3-methyl D-fucose) (R_G 0·45), obtained from *iso*emicymarin (see below). The R_G value (0·45) obtained for the sugar was identical with that of digitalose.

Examination of fractions 4, 5, *and* 6. Fraction 4, when examined by paper chromatography, proved to be a mixture of di- and mono-methyl methylfucosides with a little free methylfucoside. An attempted separation by means of cold extraction with chloroform did not give very satisfactory results, though from one monomethyl fraction an osazone, m. p. 172—176° (decomp.), which contained a methoxyl group, was obtained, indicating the presence of a free hydroxyl group on $C_{(2)}$.

Fractions 5 and 6 gave, on storage, a quantity of crystals of α-methyl-L-fucoside which were separated, drained on a tile, and recrystallised from ethyl acetate, to give m. p. 154—156°, $[\alpha]_D^{15}$ −197° (*c*, 1·1 in water) (Found: OMe, 17·2. Calc. for $C_7H_{14}O_5$: OMe, 17·4%) The remaining syrup was found, on hydrolysis with sulphuric acid (0·1N.) and examination by paper chromatography, to contain 3-methyl fucose, fucose, and a trace of hexose. Fucose estimations on these hydrolysed syrups gave: fraction (5) 93·1%; fraction (6) 87·8% calculated as fucose.

Fractionation by Solvent Extraction.—Methylated glycosides from the methylated polysaccharide (5 g.) were dissolved in water (25 c.c.) and extracted for 15·5 hours with light petroleum (b. p. 40—60°) to give fraction *A* (0·38 g.), n_D^{13} 1·4499. This fraction was distilled in a high vacuum, giving a clear syrup (0·28 g.), b. p. 83—87°/0·04 mm., n_D^{15} 1·4442 (Found: OMe, 49·8%). Extraction with chloroform for (*a*) 4½ hours gave fraction *B* (1·80 g.), n_D^{15} 1·4610 (Found: OMe, 40·0%), (*b*) 23½ hours gave fraction *C* (1·66 g.), n_D^{15} 1·4735 (Found: OMe, 28·6%), and (*c*) 34 hours gave fraction *D* (0·24 g.), partly crystalline (Found: OMe, 30·9%). Evaporation of the aqueous solution gave fraction *E* (0·97 g.) (Found: OMe, 16·4%). Recovery was 98%.

Examination of fraction A. This fraction on hydrolysis and examination by paper chromatography was found to consist of the dimethyl fucose already examined and traces of 2 : 3 : 4-trimethyl fucose and one or more highly methylated hexoses or pentoses. There was also a possible indication of the presence of a small amount of a methylated uronic acid.

Fractionation and examination of fraction B. This portion was subjected to further fractionation by passage through an alumina column (20 × 2 cm.), using for development first chloroform and then methanol. Two fractions were obtained: (*a*) with chloroform, fraction *B*1 (0·79 g.), b. p. 100—110°/0·04 mm., n_D^{16} 1·4590 [Found: OMe, 46·3%; apparent percentage of fucose (see Introduction), 32·4%], and (*b*) with methanol, fraction *B*2 (0·87 g.), n_D^{16} 1·4669 (Found: OMe, 31·1%; apparent percentage of fucose, 34·2).

Fraction *B*1 was hydrolysed with sulphuric acid (0·1N.), giving a syrup, $[\alpha]_D^{15}$ +4·6° (*c*, 3·0 in water) (Found: OMe, 32·1%), which did not crystallise even on storage for several months. Nucleation with authentic 3 : 4-dimethyl L-fucose did not induce crystallisation. Comparison of the two sugars by paper chromatography showed they had very similar R_G values (*J.*, 1950, 690), but on prolonging the experiment [48 hours in butanol–ethanol–water (40 : 10 : 50)] it was possible to differentiate between the spots after spraying with aniline oxalate.

Formation of lactone from hydrolysed fraction B1. 2 : 3-*Dimethyl* L-*fucofuranolactone*. The dimethyl fucose (0·18 g.) in water (5 c.c.) was treated with bromine (1·5 c.c.) at room temperature till non-reducing (30 hours). After aeration, neutralisation with silver carbonate, treatment with hydrogen sulphide, etc., and lactonisation, a clear syrup (0·1 g.) was obtained, having b. p. 130°/0·04 mm. (Found: OMe, 34·8%; 16 mg. required 1·67 c.c. of 0·027N-sodium hydroxide for neutralisation. $C_8H_{14}O_5$ requires OMe, 32·6%; 1·79 c.c.). The lactone showed $[\alpha]_D^{19}$ +9° (5 minutes), +10° (30 minutes), +11° (1 hour), +23° (3 hours), +28° (4 hours), +34° (8 hours), +37° (12 hours), +40° (15 hours), +47° (22 hours, constant) (*c*, 1·6 in water), the positive rotation indicating the presence of a dimethyl γ-L-fuconolactone; cf. 2 : 3 : 4-trimethyl L-fuconolactone $[\alpha]_D$ −138° ⟶ −36° (James and Smith, *loc. cit.*).

2 : 3-*Dimethyl* L-*fuconamide*. The above lactone (40·4 mg.) was treated with methanolic ammonia (2 c.c.) at 0° for 48 hours. On evaporation of the solvent at 14°/15 mm. the entire solution crystallised, giving a white solid which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 78—79°, $[\alpha]_D^{15}$ +30·2° (*c*, 0·86 in water) (Found: OMe, 30·0. $C_8H_{15}O_5N$ requires OMe, 30·3%). The *amide* gave a negative Weerman test, indicating that the hydroxyl group on $C_{(2)}$ was substituted by methoxyl.

3-*Methyl* L-*fucofuranolactone and its amide*. The hydrolysed fraction *B*2 was oxidised with bromine till non-reducing. After the usual treatment followed by lactonisation, a white crystalline product, m. p. 132—136°, was obtained. This gave $[\alpha]_D^{14}$ +25° (10 minutes), +37° (30 minutes), +46° (1 hour), +46° (2 hours), +47° (3 hours), +50° (7 hours), +53° (12 hours), +61° (19 hours), +74° (32 hours), +75° (48 hours), +75° (62 hours, constant), (*c*, 0·95 in water). This indicated a γ-lactone, and thus $C_{(4)}$ was occupied by a hydroxyl group in the methylated fucose.

The lactone gave a syrupy *amide*, $[\alpha]_D^{15}$ +17·2° (*c*, 0·6 in water) (Found: OMe, 16·7. $C_7H_{15}O_5N$ requires OMe, 16·1%). The amide (40 mg.) yielded hydrazodicarbonamide (15 mg.), m. p. 253—255° unchanged on admixture with an authentic specimen.

Paper chromatography. Examination of hydrolysed fraction *B*2 and comparison with 2-methyl L-fucose and digitalose showed that, as with fraction 3, the R_G value (0·45) was the same as that of digitalose.

Fractions C *and* D. Both fractions were observed, on hydrolysis and examination by paper chromatography, to be identical with fraction *B*2. Periodic acid oxidation of hydrolysed fraction *E* gave acetaldehyde corresponding to 34·5% of monomethyl fucose.

Derivatives from fraction C. 3-*Methyl* L-*fuconamide*. Oxidation with bromine, followed by the usual treatment, gave the lactone as a syrup, b. p. 180°/0·04 mm., n_D^{15} 1·4750 [Found: OMe, 18·1%; 14 mg. required 2·67 c.c. of 0·025N-sodium hydroxide for neutralisation. Calc. for $C_7H_{12}O_5$: OMe, 17·6%; 2·96 c.c.]. This lactone in water showed $[\alpha]_D$ +20° (20 minutes), +20° (30 minutes), +22° (1 hour), +26° (2 hours), +28° (3 hours), +29° (4 hours), +34° (6 hours), +45° (12 hours), +50° (18 hours), +52° (21 hours), +59° (28 hours), +67° (36 hours), +74° (42 hours, constant) (*c*, 0·7 in water). 2 C.c. of the above solution required 2·66 c.c. of 0·02505N-sodium hydroxide (Calc.: 2·96 c.c.).

Treatment of the above lactone with methanolic ammonia gave a crystalline *amide*, m. p. 176—180°, $[\alpha]_D^{14}$ +16·4° (*c*, 0·58 in water) (Found: OMe, 16·4. $C_7H_{15}O_5N$ requires OMe, 16·1%). This amide (43 mg.) gave hydrazodicarbonamide (20 mg.), m. p. 256° (decomp.) unchanged on admixture with an authentic speciman.

Fraction E. *Isolation of α-methyl* L-*fucoside*. This fraction partly crystallised, and after drying on a porous tile and recrystallisation from ethyl acetate had m. p. 154—155° not depressed on admixture with authentic α-methyl-L-fucoside, $[\alpha]_D^{15}$ −194° (*c*, 1·1) (Found: OMe, 17·0. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). Examination by paper chromatography after hydrolysis showed the fraction to consist of fucose with a trace of a hexose. A fucose estimation with periodic acid gave 90·3% fucose.

Extraction of 3-*Methyl* D-*Fucose from* iso*Emicymarin*.—The cardiac glycoside emicymarin is a much better source of digitalose (3-methyl D-fucose), but unfortunately no samples of this compound were available.

*iso*Emicymarin (0·3 g.), obtained through the kindness of Dr. S. Smith, Wellcome Chemical Research Laboratories, Beckenham, was dissolved in 50% alcohol (150 c.c.) containing 5% of hydrochloric acid and hydrolysed for 4 hours on a boiling water-bath. After extraction several times with chloroform, the aqueous fraction was neutralised with silver carbonate. Removal of the silver salts and evaporation gave a small yield of syrup (60 mg.).

Preparation of 3-*Methyl* D-*Fuconolactone*.—Part of the syrup (54 mg.) was oxidised with bromine for 3 days. After the usual treatment and lactonisation a small amount of needle-shaped crystals, m. p. 136—140°, was obtained. This gave $[\alpha]_D^{13}$ −22° (5 minutes), −24° (1 hour), −27° (3 hours), −31° (5 hours), −35° (9 hours), −38° (12 hours), −45° (17 hours), −53° (24 hours), −63° (36 hours), −68° (42 hours), −70° (60 hours, constant) (*c*, 0·9 in water).

Oxidation of Fucoidin with Sodium Periodate [*with* A. G. Ross].—Fucoidin (0·520 g.) from *Himanthalea lorea* (see Part I, *loc. cit.*) was dissolved in sodium metaperiodate solution (40 c.c.; 0·1M.) and continuously shaken. Samples (5 c.c.) were removed at intervals and the remaining periodate estimated, after 15 minutes, with iodine (0·1N.) after the addition of sodium hydrogen carbonate (1 g.), sodium arsenite (20 c.c.; 0·1N.), and potassium iodide (1 g.) (Found: uptake of sodium periodate in g.-equivs./100 g. of fucoidin, 4 hours 0·088, 24 hours 0·131).

Thanks are expressed to the Scottish Seaweed Research Association for the provision of seaweed samples, to Dr. S. Smith for the gift of *iso*emicymarin, and to Imperial Chemical Industries Limited for grants.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, December* 13*th*, 1949.]

168. *Decomposition Reactions of the Aromatic Diazo-compounds. Part XII. The Reaction between Diazo-compounds and Potassium Ferrocyanide.*

By M. C. Ford, William A. Waters, and H. T. Young.

The conditions under which aromatic diazo-compounds react with potassium ferrocyanide solution to yield arylazodiaryls have been studied, and it has been found that the decomposition proceeds most smoothly at pH 4—5 in the presence of a sodium acetate buffer. Yields of about 20% can be obtained with substituted aromatic amines, $R\cdot C_6H_4\cdot NH_2$, when the substituent R = Me or Cl, but both with the strongly *op*-directive substituent OMe and with the *m*-directive substituent NO_2 the yield falls to under 0·5%.

Both degradative and synthetic reactions have been carried out to establish the structures of the unsymmetrical arylazodiaryls obtained from *o*- and *p*-toluidine, *p*-chloroaniline, and α-naphthylamine. When the substituent R occupies the *p*-position to the nitrogen in the original amine, the reaction product is the 2-aryl derivative of a 4 : 4′-substituted azobenzene, and when R is an *o*-substituent the product is a 4-aryl derivative of a 2 : 2′-substituted azobenzene. Isomeric reaction products do not appear to be formed in appreciable amount. Possible mechanisms of this reaction are discussed.

In Part XI (*J.*, 1946, 1154) Saunders and Waters drew attention to the fact that 4-phenylazobenzene (I; R = H) can be prepared by treating aqueous solutions of benzenediazonium salts with potassium ferrocyanide, and suggested that free phenyl radicals might play some part in this rather unusual diazo-decomposition. We have now made an experimental study of this reaction, which since its discovery by Griess (*Ber.*, 1876, **9**, 132) has received scarcely any attention during this century, and we have established the structures of the unsymmetrical arylazodiaryls which can be prepared from diazotised *o*- and *p*-toluidine, *p*-chloroaniline, and α-naphthylamine.

The account given by Griess is very brief, and it was left to Locher (*Ber.*, 1888, **21**, 911) to show that Griess's reaction product, $C_{18}H_{14}N_2$, m. p. 150°, was probably 4-phenylazobenzene since it could be reduced to a mixture of aniline and *p*-aminodiphenyl (m. p. 50—51°). We have confirmed this work and have obtained from Griess's azo-compound pure *p*-acetamidodiphenyl having a melting point which was unchanged after admixture with an authentic specimen.

On investigating the conditions under which 4-phenylazobenzene can be obtained from aqueous solutions of benzenediazonium sulphate or chloride and potassium ferrocyanide, we found that, though the evolution of nitrogen commences immediately the reactants are mixed at, or below, room temperature, the yield of the desired reaction product is greatly increased by first buffering the diazonium salt solution to pH 4—5 by addition of an excess of sodium acetate. However, if the diazo-solution is first made neutral with sodium hydroxide or sodium hydrogen carbonate, only tarry products result. The organic reaction product usually separates as a filterable solid as the nitrogen is evolved. The reaction can in every case be completed at room temperature and it leaves a purple or brown aqueous solution which does not couple with alkaline β-naphthol. In some cases there was an indication that an intermediate solid diazonium ferrocyanide may be formed. After the reaction is over, the aqueous solution contains ferricyanide anions, showing that the reaction is essentially a reduction of the aromatic diazo-compound. The yields of the desired organic products were not appreciably altered by changing from the procedure of adding aqueous potassium ferrocyanide to a stirred buffered solution of benzenediazonium sulphate to the reverse procedure of adding the diazo-solution to the stirred ferrocyanide (contrast the Sandmeyer reaction), and so for convenience the second procedure was generally used with the other diazonium compounds.

When working with diazotised aniline and *p*-toluidine, there was no advantage in taking much more potassium ferrocyanide than the amount indicated by the simplified equation

$$3R\cdot C_6H_4\cdot N_2^+ + 2[Fe(CN)_6]^{4-} \longrightarrow R\cdot C_6H_4\cdot C_6H_3R\cdot N_2\cdot C_6H_4R + H^+ + 2[Fe(CN)_6]^{3-}$$

but when working with diazotised *p*-chloroaniline the yield of arylazodiaryl could be almost doubled by using 2 moles of ferrocyanide per mole of diazo-compound. In no case, however, was the overall yield of pure material more than 20%.

The products remaining in the aqueous layer were regularly investigated. These solutions invariably smelt of *iso*cyanide and, when heated, deposited Prussian-blue. On steam-distillation, however, they yielded only very small amounts of the nitriles, $R\cdot C_6H_4\cdot CN$, corresponding to the original amines, and no detectable amounts of the corresponding phenols,

$R{\cdot}C_6H_4{\cdot}OH$, or of hydrocarbons $R{\cdot}C_6H_4{\cdot}H$ or $R{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}R$. Small amounts of hydroxyazo-dyes were always formed. When diazonium chlorides are used instead of diazonium sulphates no significant quantities of aryl chlorides can be detected. Hence this diazo-reaction does not correspond with the normal decomposition of a diazonium cation in water: $Ar{\cdot}N_2^+ + H_2O \longrightarrow Ar{\cdot}OH + H^+$ (cf. Part X, *J.*, 1942, 266, for Type I reactions of the aromatic diazo-compounds), and is not clearly related to the Sandmeyer reaction which Cowdrey and Davies (*J.*, 1949, S 48) have recently shown to be an intramolecular decomposition of a complex salt. It is therefore probable that the initial reaction which involves the oxidation of the ferrocyanide anion is a one-electron transfer, as indicated in equations (1*a*) and (1*b*), and that the final azo-compounds result from reactions involving free organic radicals. The recent demonstration by Merz and Waters (*J.*, 1949, 2427) that free aryl radicals do not react with water molecules adds support to this view.

(1*a*) $$Ar{\cdot}N_2^+ + [Fe(CN)_6]^{4-} \longrightarrow Ar{\cdot}N_2{\cdot} + [Fe(CN)_6]^{3-}$$

or

(1*b*) $$Ar{\cdot}N{:}N{\cdot}OH + [Fe(CN)_6]^{4-} \longrightarrow Ar{\cdot}N_2{\cdot} + (OH)^- + [Fe(CN)_6]^{3-}$$

followed by

(2) $$Ar{\cdot}N{:}N{\cdot} \longrightarrow Ar{\cdot} + N_2$$

As suggested in Parts X and XI, electron-transfer potentials may be significant in determining yields in reactions such as (1) above, and in this connection it was observed that the yield of isolatable arylazodiaryl became very small indeed when the selected aromatic diazo-compound contained either a strongly electron-donating $(+T)$ substituent such as methoxyl, or a strongly electron-abstracting $(-I, -T)$ substituent such as the nitro-group. From diazotised *p*-anisidine only a small yield of an intractable tar containing a little azoanisole was obtained; from diazotised *p*-nitroaniline the yield of arylazodiaryl dropped to 0·2% and no 4 : 4′-dinitroazobenzene could be identified, though tarry hydroxyazobenzene derivatives were formed in quantity.

The elucidation of the structures of the azo-compounds obtained from substituted aromatic amines yielded information of considerable interest. Griess (*loc. cit.*) in his account of the reaction between benzenediazonium nitrate and potassium ferrocyanide reported that the solid product, $C_{18}H_{14}N_2$, was mixed with a little azobenzene, which he separated by steam-distillation, and also with a " red oil " of unknown constitution. This red oil was later studied by Ehrenpreis (*Chem. Zentr.*, 1907, I, 1789), who reduced it to a product of m. p. 135—138° which he believed to be triphenylhydrazine, and reported that it gave an acetyl derivative of m. p. 152°. Both Busch and Holbein (*Ber.*, 1907, **40**, 2099) and Wieland and Reverdy (*Ber.*, 1915, **48**, 1112), however, have shown that triphenylhydrazine does not have these properties. Ehrenpreis's compounds may perhaps be semidine derivatives. We have examined further the red oil which remains as the mother-liquor from the crystallisation of 4-phenylazobenzene (I; R = H) from the crude product of the Griess reaction, and have found that on distillation at low pressures it yields a considerable proportion of azobenzene and leaves a residue from which more 4-phenylazobenzene can be separated. We have also attempted to separate chromatographically further components of this oil, and have carried out repeated fractional crystallisations. In consequence of all our work we conclude that it is essentially a mixture of 4-phenylazobenzene with azobenzene, and, in particular, that no appreciable quantities of any isomers of 4-phenylazobenzene are present.

Locher (*loc. cit.*), who carried out the ferrocyanide decomposition with diazotised toluidines and with diazotised α-naphthylamine, reported that *o*-toluidine gave a " *o*-ditolyl-*o*-azotoluene " of m. p. 104°. We have now found that this product separates in a comparatively pure state, in 22% yield, from the reaction mixture together with about 1% of 2 : 2′-azotoluene * and a very little *o*-tolunitrile. Isomers of Locher's product were sought, but none found. The main reaction product has the structure of 4-*o*-tolyl-2 : 2′-azotoluene (I; R = Me) since it could be reduced to a mixture of *o*-toluidine and an aminoditolyl (II). The latter gave *o*-toluic acid on chromic acid oxidation (thus confirming the orientation in ring B), and on bromination at room temperature it gave only a monobromo-derivative, so that the two substituents in ring A must occupy *o*- and *p*-positions to the amino-group. Nitration with copper nitrate and acetic anhydride (Menke, *Rec. Trav. chim.*, 1925, **44**, 141; Waters, *J.*, 1935, 1875) of the acetyl derivative of the base (II), followed by hydrolysis, yielded an *o*-nitro-amine, since it was successfully reduced to a diamine which condensed with phenanthraquinone to give a phenazine derivative. Assuming that the *o*-tolyl configuration is retained

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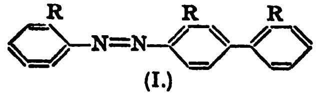
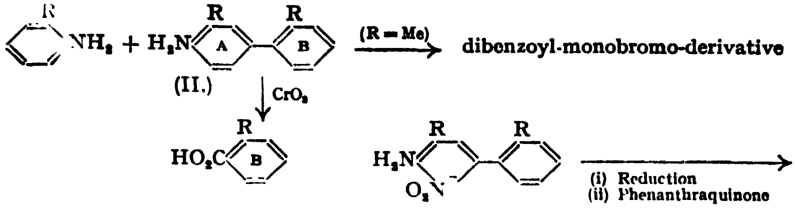
* In the azotoluenes the prefixed numerals refer to the positions of the methyl groups.

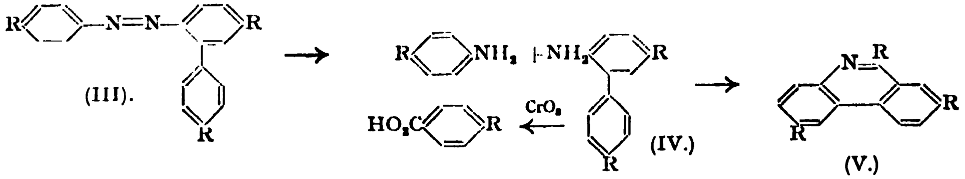
in regard to the methyl group in ring A of the base (II), it follows that the original " *o*-ditolyl-*o*-azotoluene " can only have the structure (I).



(I.)



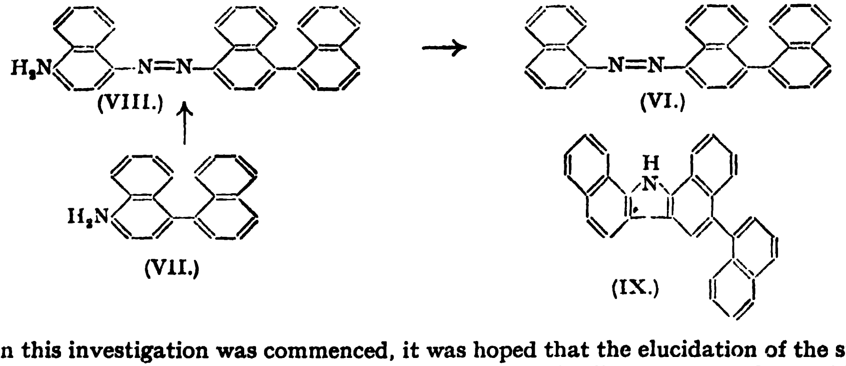
From diazotised *p*-toluidine Locher isolated a " *p*-ditolyl-*p*-azotoluene " of m. p. 118°; we found that this compound is mixed with small quantities of 4 : 4′-azotoluene and of *p*-tolunitrile, and that it is not accompanied by significant amounts of any isomers. The product is 2-*p*-tolyl-4 : 4′-azotoluene (III; R = Me) since reduction gave *p*-toluidine together with an aminoditolyl (IV; R = Me) which (i) was oxidised to *p*-toluic acid, (ii) yielded only a mono-bromo-derivative in the cold, and (iii) gave an acetyl derivative which could be condensed to 3 : 7 : 9-trimethylphenanthridine (V; R = Me). Morgan and Walls (*J.*, 1930, 1507) obtained the same amine (IV; R = Me) by pyrolysis of diazoamino-*p*-toluidine and established its structure by conversion into 2 : 6-dimethylcarbazole, which they then synthesised by another route.



Diazotised *p*-chloroaniline, with which this reaction had not previously been performed, yielded the analogous product, 4 : *4′-dichloro-*2-*p*-*chlorophenylazobenzene* (III; R = Cl) with which again the reaction sequence given in the diagram above was successfully carried out. The main reaction product was, in this case, isolated by extraction (Soxhlet) with light petroleum of the bulky brown material which separates from the aqueous reaction mixture. There remains an insoluble residue which exhibits reactions indicative of a polyazo-compound but does not appear to contain isomers of (III). Again, small amounts of 4 : 4′-dichloroazobenzene and of *p*-chlorobenzonitrile were formed. *p*-Nitroaniline gives a similar product [probably (III; R = NO_2)] but only in 0·2% yield. Unfortunately, its structure cannot be established by the same reaction sequence, since reduction would also affect the nitro-groups.

From diazotised α-naphthylamine Locher obtained 1 : 1′-azonaphthalene and another substance. We found that this second compound can be extracted from the solid reaction product in about 9% yield, and it proves to be 4-α-naphthyl-1 : 1′-azonaphthalene (VI). It was synthesised by reducing 4-nitro-1 : 1′-dinaphthyl (Schoepfle, *J. Amer. Chem. Soc.*, 1923, **45**, 1566) to the corresponding *amine* (VII), coupling this with α-naphthylamine and then deaminating the resulting azo-dye (VIII). Reduction of (VI) was also attempted, but the reaction product proved to be 3-α-naphthyl-1 : 2 : 7 : 8-dibenzcarbazole (IX) and not the amine (VII). The production of a dibenzcarbazole derivative affords confirmatory evidence of the structure (VI) of the azo-compound, since carbazole formation can only occur if both β-positions adjacent to the azo-group are unsubstituted.

It will be seen, therefore, that in all these reactions between substituted aromatic diazo-compounds and potassium ferrocyanide an azobenzene derivative is formed in which an aryl residue occupies the *p*-position to the azo-group whenever possible. If this position is blocked in the original amine, the aryl residue occupies the *o*-position to the azo-group. Neither isomers nor symmetrical diarylazodiaryl derivatives appear to be formed. Furthermore, the nitrogen atoms of the substituted bases, $R{\cdot}C_6H_4{\cdot}NH_2$, retain throughout their original orientations relative to the group R, and the whole distinctive reaction can be viewed as an aromatic substitution by a $R{\cdot}C_6H_4{\cdot}$ group.


(VIII.)

(VII.)

(VI.)

(IX.)

When this investigation was commenced, it was hoped that the elucidation of the structures of the arylazodiaryls obtainable from substituted aromatic diazo-compounds would help to establish whether the substituting aryl group reacts in the form of a cation or of an electrically neutral radical, but as yet no clear discrimination between plausible alternatives can be made.

Our results show that arylation has occurred in the *p*- or *o*-position to an azo-, or diazo-, group, and not in the *p*- or *o*-position to electron-donating substituents such as Me or Cl. However, since only 1—2% of the simple arylazoaryl compounds could be isolated in comparison with 10—20% of arylazodiaryls, it is improbable that our reaction proceeds by way of arylation of a symmetrical azobenzene derivative, and indeed an attempt to phenylate azobenzene in acetone solution (cf. Part VI, *J.*, 1939, 870) failed. The most probable alternatives therefore require that the diaryl group should be formed at an early stage of the reaction, *i.e.*:

(*a*) By arylation of a diazonium cation:

$$R{\cdot}C_6H_4{\cdot} + (R{\cdot}C_6H_4{\cdot}N_2)^+ \longrightarrow (R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N_2)^+ + H^+$$

followed by

$$(R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N_2)^+ + R{\cdot}C_6H_4{\cdot} + e \longrightarrow R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N{:}N{\cdot}C_6H_4R$$

or (*b*) by arylation of a covalent diazo-hydroxide:

$$R{\cdot}C_6H_4{\cdot} + R{\cdot}C_6H_4{\cdot}N{:}N{\cdot}OH \longrightarrow R{\cdot}C_6H_4{\cdot}C_6H_3R{\cdot}N{:}N{\cdot}OH + H{\cdot}$$

Though the radical-type reactions suggested above seem to afford the best interpretation of our experimental work because of the absence of significant percentages of phenolic products (see p. 834) diagnostic of the presence of aryl cations, we nevertheless cannot exclude entirely cationoid substitutions by aryl ions because the observed *op*-substitution of azo-compounds is characteristic also of reactions involving cationoid attack. Thus 4 : 4′-dichloroazobenzene and 4 : 4′-azotoluene are both nitrated in position 2, adjacent to the $\cdot N{:}N\cdot$ group (see Houghton and Waters, *J.*, in the press). We would point out, however, that the simple polar substitution of a benzenediazonium cation, *i.e.*,

$$Ar^+ + (C_6H_5{\cdot}N_2)^+ \longrightarrow \text{products}$$

should give a *m*-substituted product (cf. the nitration of phenyltrimethylammonium salts) and this certainly is not formed.

EXPERIMENTAL.

Preparation of 4-Phenylazobenzene.—Aniline (23 g.), dissolved in hydrochloric acid (82 ml.) and water (50 ml.), was diazotised at 0—5° with sodium nitrite (18 g.) in water (50 ml.), and the resulting solution was buffered with a solution of sodium acetate (100 g.) in water (200 ml.). This cold solution was then added slowly to a stirred solution of potassium ferrocyanide (125 g.) in water (600 ml.) at room temperature. A dark red precipitate of benzenediazonium ferrocyanide formed at once, and decomposed gradually with evolution of nitrogen. The mixture was kept overnight, and the resulting brown solid was then collected, washed thoroughly with water and dilute alkali, and fractionally crystallised from alcohol (charcoal). In this way 4·4 g. (22%) of 4-phenylazobenzene were obtained in the form of orange-yellow crystals, m. p. 152° (Found: C, 83·6; H, 5·3; N, 10·9. Calc. for $C_{18}H_{14}N_2$: C, 83·75; H, 5·4; N, 10·9%). When the benzenediazonium ferrocyanide was separated at once it decomposed to give only a black tar.

The residue from the crystallisation of the 4-phenylazobenzene was a red oil which on distillation at 0·5 mm. pressure yielded 1% of azobenzene and a little more phenylazobenzene.

The aqueous filtrate from the reaction smelt strongly of phenyl *iso*cyanide. On distillation with steam it yielded a little azobenzene but not phenol, and a bulky precipitate of Prussian-blue separated.

When sodium acetate was not added the yield of 4-phenylazobenzene was only about 1%. Neutralisation of the benzenediazonium sulphate or chloride with sodium hydroxide or sodium hydrogen carbonate solutions led to formation of very tarry products.

Reduction of 4-phenylazobenzene with tin and alcoholic hydrochloric acid gave a mixture of aniline and 4-aminodiphenyl; from the latter, 4-acetamidodiphenyl, m. p. and mixed m. p. with an authentic specimen, 167°, was obtained.

4-o-*Tolyl*-2 : 2′-*azotoluene* (I; R = Me).—A solution of *o*-toluidine (1 mol.) in ice-cold 20% hydrochloric acid (540 ml., 3 mols.) was diazotised at 0—5° with sodium nitrite solution (75 g. in 200 ml. of water) and the product was buffered with a solution of hydrated sodium acetate (272 g., 2 mols.) in water (225 ml.). The resulting solution was slowly added to a mechanically stirred solution of potassium ferrocyanide (840 g., 2 mols.) in water (3 l.). Nitrogen was evolved gradually. After the mixture had been left overnight, the resulting red precipitate was collected and recrystallised from ethyl alcohol; yield, 22%. The pure product separated in orange-red platelets from methyl alcohol and had m. p. 105·5° (Ehrenpreis gives 104°) (Found : C, 84·2; H, 6·2; N, 9·2. Calc. for $C_{21}H_{20}N_2$: C, 84·0; H, 6·7; N, 9·3%).

The mother-liquors from the recrystallisations were combined, the solvent removed, and the residue distilled in a vacuum. From the combined residues from 5 mols. of *o*-toluidine there were obtained : (i) 0·5 g. of *o*-tolunitrile, b. p. 40°/1·5 mm., identified by hydrolysis to *o*-toluic acid, m. p. and mixed m. p. 103°, and (ii) 5 g. of 2 : 2′-azotoluene, m. p. and mixed m. p. 54°.

Reduction. A solution of the azo-compound (20 g.) in boiling alcohol (500 ml.) was added portionwise to a solution of stannous chloride (112 g. of hydrate) in concentrated hydrochloric acid (112 ml.) at 100°. Each portion was immediately decolorised. (Note. Addition of stannous chloride solution to the azo-compound was unsatisfactory, as it gave an intractable mixture of involatile amines, possibly of semidine type.) The alcohol was removed from the completely reduced solution under diminished pressure, the residue was made strongly alkaline with sodium hydroxide and extracted with ether, and the bases were collected and distilled in a vacuum giving : (i) *o*-toluidine (2·5 g.), identified as its acetyl and benzoyl derivatives, and (ii) 4-amino-3 : 2′-ditolyl (7·1 g.), b. p. 92°/0·005 mm. This was a pale yellow viscous oil which rapidly darkened on storage. Its *acetyl* derivative crystallised from light petroleum (b. p. 60—80°) in fine matted needles, m. p. 143° (Found : C, 80·5; H, 7·22; N, 5·6. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·8%). Its *dibenzoyl* derivative, prepared by treating the base with an excess of benzoyl chloride in boiling pyridine, crystallised from alcohol in short needles, m. p. 140·5° [Found : C, 83·1; H, 5·7; N, 3·4%; *M* (Rast), 393. $C_{28}H_{23}O_2N$ requires C, 82·9; H, 5·7; N, 3·45%; *M*, 405]. Under the same conditions it was found that *N*-dibenzoyl derivatives were obtained from other *o*-substituted amines, including *o*-toluidine itself. The *picrate* of the base crystallised in stout yellow prisms, m. p. 198° (Found : N, 13·2. $C_{20}H_{18}O_7N_4$ requires N, 13·1%).

A portion of the base was oxidised with chromic acid in aqueous acetic acid solution and gave *o*-toluic acid, m. p. and mixed m. p. 102—103°. Another portion (2·0 g.) was dissolved in glacial acetic acid (50 ml.) containing anhydrous sodium acetate (2·5 g.) and a 3% solution of bromine in glacial acetic acid was added dropwise. When just over one molar equiv. (60 ml.) had been added free bromine remained in the solution. To ensure completion of the reaction a slight further excess of bromine was added, and after 5 minutes the mixture was poured into dilute alkaline sodium sulphite solution. The purple oily 5-bromo-4-amino-3 : 2′-ditolyl was collected. From a small part the *hydrochloride* was prepared and crystallised from alcoholic hydrochloric acid in glistening needles, m. p. 160° (decomp.) (Found : Cl + Br, 34·4. $C_{14}H_{14}NBr,HCl$ requires Cl + Br, 36·8%). The remainder was benzoylated as described above, and yielded 5-*bromo*-4-*dibenzamido*-3 : 2′-*ditolyl*, which crystallised from alcohol in rosettes of needles, m. p. 175° (Found : C, 69·4, 69·3*; H, 4·8, 4·7*; N, 3·0%; *M*, 485. $C_{28}H_{22}O_2NBr$ requires C, 69·5; H, 4·6; N, 2·9%; *M*, 484) (* denotes macro-analysis by Mr. F. C. Hall).

Nitration of 4-*Acetamido*-3 : 2′-*ditolyl.*—Powdered hydrated copper nitrate (7 g.) was added in small portions to a stirred suspension of acetamidoditolyl (10·5 g.) in acetic anhydride (50 ml.), kept at 25—30° in a bath of cold water. After an hour the clear green solution was poured into water, and the pale yellow 5-nitro-4-acetamido-3 : 2′-ditolyl (90%) was collected and hydrolysed by refluxing for 6 hours with a 30% solution of sulphuric acid in ethyl alcohol. After removal of the alcohol, the residue was poured into water and the resulting 5-*nitro*-4-*amino*-3 : 2′-*ditolyl* was crystallised repeatedly from aqueous methyl alcohol. It formed long orange needles, m. p. 95° (Found : C, 69·3; H, 5·9; N, 11·5. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

This base (0·5 g.) was reduced with an excess of zinc dust in boiling glacial acetic acid solution (25 ml.), and the purple solution was filtered into a solution of phenanthraquinone (0·4 g.) in hot glacial acetic acid (10 ml.). After the mixture had been heated for an hour it was poured into water, and a black powder separated. This was dissolved in acetone and passed down a column of activated alumina. On precipitation with water the eluted liquid gave a brown powder which was collected and crystallised repeatedly from benzene–light petroleum (b. p. 40—60°), to give eventually 12-o-*tolyl*-10-*methylphenanthrazine* (8-o-*tolyl*-6-*methyl*-1 : 2 : 3 : 4-*dibenzphenazine*) as very small light-brown needles, m. p. 192—193° (Found : C, 86·9; H, 5·0; N, 7·2. $C_{28}H_{20}N_2$ requires C, 87·4; H, 5·2; N, 7·3%). This substance gave a brilliant purple solution in concentrated sulphuric acid.

2-p-*Tolyl*-4 : 4′-*azotoluene*.—A diazotised solution of *p*-toluidine (1 mol.) was buffered with sodium acetate, as described above, and added slowly with stirring to a solution of potassium ferrocyanide (1 mol.) in water (1½ l.). A red diazonium ferrocyanide was precipitated, but quickly decomposed with evolution of nitrogen, leaving a dark brown solid and an aqueous liquid which did not react with alkaline β-naphthol. The solid (yield, 55—60%) was collected and extracted with hot alcohol. The tarry product was crystallised repeatedly from light petroleum (b. p. 60—80°) and then alcohol, to give pure 2-*p*-tolyl-4 : 4′-azotoluene in 10% yield, together with a much smaller amount of 4 : 4′-azotoluene, m. p. and mixed m. p. 142°. Attempts to isolate other products from the residual tar were not successful. The main product had m. p. 118°, in agreement with Ehrenpreis (Found : C, 83·7; H, 6·7; N, 9·6. Calc. for $C_{21}H_{20}N_2$: C, 84·0; H, 6·7; N, 9·3%).

The azo-compound was reduced with stannous chloride in alcoholic hydrochloric acid, and, after removal of the excess of alcohol, the solution was made alkaline and distilled in steam. *p*-Toluidine collected in the receiver as a white solid; its identity was confirmed. The remaining liquid was cooled, extracted with ether, and the *2-amino-5 : 4′-ditolyl* which had been formed was finally purified by distillation in a vacuum (b. p. 123—128°/0·4 mm.) (Found : C, 85·2; H, 7·6; N, 7·5. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%). Its acetyl derivative crystallised from aqueous alcohol in long needles, m. p. 104° (Found : C, 80·3; H, 7·1; N, 5·6. Calc. for $C_{16}H_{17}ON$: C, 80·3; H, 7·1; N, 5·9%), and its *benzoyl* derivative formed white needles, m. p. 122° (Found : C, 83·4; H, 6·5; N, 4·8. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·3; N, 4·7%). On treatment for 20 minutes with concentrated nitric acid, the acetyl derivative yielded a dinitro-compound, probably *3 : 2′-dinitro-2-acetamido-5 : 4′-ditolyl*, which crystallised from very dilute alcohol in yellow needles, m. p. 191° (Found : C, 58·7; H, 4·8; N, 13·0. $C_{16}H_{15}O_5N_3$ requires C, 58·4; H, 4·6; N, 12·8%).

On oxidation with chromic acid in aqueous acetic acid the 2-amino-5 : 4′-ditolyl (1 g.) gave *p*-toluic acid (0·2 g.), m. p. and mixed m. p. 177°.

3-Bromo-2-amino-5 : 4′-ditolyl.—2-Amino-5 : 4′-ditolyl (1 g.) was dissolved in carbon tetrachloride (20 ml.), a little powdered sodium acetate was added, and a 1% solution of bromine in carbon tetrachloride was slowly run into the mixture, cooled in ice. When excess of bromine was present, aqueous sulphurous acid was immediately stirred in to prevent further conversion into dark products. The carbon tetrachloride layer after separation, washing with water, and evaporation gave a dark residue from which white crystals of the *bromo*-base were obtained by crystallisation from aqueous methyl alcohol (charcoal); m. p. 68° (Found : C, 60·7; H, 5·1; Br, 28·8. $C_{14}H_{14}NBr$ requires C, 60·9; H, 5·1; Br, 28·9%). Its *acetyl* derivative crystallised from aqueous alcohol in white needles, m. p. 135° (Found : C, 60·2; H, 4·9. $C_{16}H_{16}ONBr$ requires C, 60·4; H, 5·0%), and its *monobenzoyl* derivative, prepared by the Schotten–Baumann method, formed white needles, m. p. 195° (Found: C, 66·0; H, 4·6. $C_{21}H_{18}ONBr$ requires C, 66·5; H, 4·5%).

3 : 7 : 9-Trimethylphenanthridine.—2-Acetamido-5 : 4′-ditolyl (1·3 g.) and phosphorus oxychloride (3 g.) were heated under reflux in nitrobenzene solution (15 ml.) with the addition of a drop of stannic chloride as catalyst. After 4 hours the evolution of hydrogen chloride had ceased. The mixture was then poured into water, nitrobenzene was removed by distillation in steam, and the remaining solid, consisting of the hydrochloride of 3 : 7 : 9-trimethylphenanthridine, was collected and crystallised from alcohol containing a little hydrochloric acid. It formed pale yellow felted needles which did not melt below 250°. The free *base* was prepared from this and purified by crystallisation from light petroleum (b. p. 60—80°); yield, 60%. It formed pale yellow prisms, m. p. 123° (Found : C, 87·0; H, 6·8; N, 6·4. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%).

*4 : 4′-Dichloro-2-*p*-chlorophenylazobenzene* (III; R = Cl).—*p*-Chloroaniline (42·5 g., 0·33 mol.) in 25% hydrochloric acid (150 ml., 1 mol.) was diazotised below 5°, buffered with sodium acetate (91 g., 0·66 mol.) in water (75 ml.), and slowly added, with mechanical stirring, to a solution of potassium ferrocyanide (280 g., 0·66 mol.) in water (1 l.). Evolution of nitrogen was immediate and rapid and a few drops of butyl alcohol had to be added to control foaming. After the mixture had been left overnight, the light-brown precipitate was collected, dried (yield, 60%), and extracted thoroughly with light petroleum (b. p. 60—80°). A yellow crystalline solid was obtained, together with tar. By repeated crystallisation from acetic acid and then acetone the former gave, in 13% yield, pale yellow felted needles of *4 : 4′-dichloro-2-*p*-chlorophenylazobenzene*, m. p. 153° (Found : C, 60·2; 59·9; H, 3·2, 3·3; N, 7·8, 7·6; Cl, 29·4. $C_{18}H_{11}N_2Cl_3$ requires C, 59·8; H, 3·0; N, 7·8; Cl, 29·5%). The red tarry residue was evaporated and distilled in a vacuum. It gave a trace of *p*-chlorobenzonitrile, and then, at 120—170°/0·5 mm., an orange oil which solidified, and gave, on recrystallisation, orange needles of 4 : 4′-dichloroazobenzene (1%), m. p. and mixed m. p. 183°. Steam-distillation of the aqueous liquid from the initial reaction gave a further small quantity of *p*-chlorobenzonitrile, identified by hydrolysis to *p*-chlorobenzoic acid, m. p. and mixed m. p. 232°.

Reduction. 4 : 4′-Dichloro-2-*p*-chlorophenylazobenzene (10 g.) in boiling glacial acetic acid was treated, in portions, with zinc dust (15 g.). To complete the reduction a mixture of hydrochloric acid (5 ml.) in acetic acid (20 ml.) was subsequently added. The colourless solution was filtered hot, concentrated, and made strongly alkaline with 50% sodium hydroxide solution. The bases were extracted with ether, this solvent was removed, and the residue was extracted at 80° with five successive portions of hot water. The aqueous extract, on cooling, deposited *p*-chloroaniline (0·8 g.), identified by its acetyl and benzoyl derivatives (m. p.s and mixed m. p.s with authentic specimens 177° and 191°, respectively). The residue was a sticky product, and, since attempts at crystallisation failed, it was benzoylated in pyridine solution, and the benzoylated amines were fractionally crystallised from aqueous alcohol. *5 : 4′-Dichloro-2-benzamidodiphenyl* (2 g.) was thus obtained in white needles, m. p. 191° (Found : C, 66·7; H, 4·4; N, 4·0. $C_{19}H_{13}ONCl_2$ requires C, 66·7; H, 3·8; N, 4·1%) (C and H analysis by Mr. G. Ingram).

A small portion of the crude base was oxidised with chromic acid in acetic acid solution and gave *p*-chlorobenzoic acid, m. p. and mixed m. p. 232° (anilide, m. p. 195°).

3 : 7-Dichloro-9-phenylphenanthridine.—5 : 4′-Dichloro-2-benzamidodiphenyl (1 g.) and phosphorus oxychloride (3 g.) were heated under reflux for 6 hours in nitrobenzene solution (10 ml.) together with a few drops of stannic chloride. A further ml. of phosphorus oxychloride was then added, and the heating continued for another 10 hours. The product was poured into water and steam-distilled, and the solid residue was collected and recrystallised from alcoholic hydrochloric acid, yielding pale yellow needles of the hydrochloride of the phenanthridine. The free *base*, obtained by treating the salt with aqueous ammonia and extraction with ether, crystallised from benzene in colourless needles, m. p. 193°, not identical with those of the original dichlorobenzamidodiphenyl (m. p. 191°); yield, 50% (Found : C, 69·9; H, 3·6; N, 4·4. $C_{19}H_{11}NCl_2$ requires C, 70·4; H, 3·4; N, 4·3%) (C and H analysis by Mr. G. Ingram). This base gave a *picrate*, which crystallised from benzene in mustard-yellow needles, m. p. 220° (Found : N, 9·9. $C_{25}H_{14}O_7N_4Cl_2$ requires N, 10·1%). The ultra-violet absorption spectrum of the base in methyl-alcoholic solution (maxima at 2600, 3410, and 3575 A.) accorded with the phenanthridine structure.

4 : *4′-Dinitro-2-*p*-nitrophenylazobenzene.*—*p*-Nitroaniline (46 g.) and sodium nitrite (25 g.) were ground to a smooth paste with water (100 ml.) and poured on a mixture of ice (100 g.) and concentrated hydrochloric acid (100 ml.). After being stirred for 10 minutes, the mixture was filtered into a solution of sodium acetate (91 g.) in water (100 ml.), and the product was slowly added to a mechanically stirred solution of potassium ferrocyanide (280 g.) in water (1 l.). A few drops of butyl alcohol were added to moderate the foaming which occurred. After the mixture had been left overnight, the black precipitate was collected, dried, and extracted with absolute alcohol (Soxhlet). The alcohol was then removed, the residue was boiled with 10% sodium hydroxide solution to remove hydroxyazo-compounds, and the alkali-insoluble residue was crystallised repeatedly from acetone and then from xylene. It gave the 4 : *4′-dinitro-2-*p*-nitrophenylazobenzene* as a brick-red powder, m. p. 240° (decomp.) (yield, ½%) (Found : N, 18·0. $C_{18}H_{11}O_6N_5$ requires N, 17·8%). In admixture with authentic 4 : 4′-dinitroazobenzene (m. p. 219°) (Calc. : N, 20·6%) the m. p. was lowered to 203°. When this was boiled with alcoholic ammonium sulphide and the product made strongly alkaline, an intense grass-green colour was produced. Under the same conditions 4 : 4′-dinitroazobenzene gave an intense blue colour.

The reaction described above for *p*-toluidine was repeated with *p*-anisidine. The product was a sticky tar from which by repeated crystallisation from methyl alcohol, yellow 4 : 4′-azoanisole, m. p. and mixed m. p. 158—159°, was eventually isolated in ½% yield, together with anisonitrile, m. p. 46°, in ¼% yield.

4-α-*Naphthyl*-1 : 1′-*azonaphthalene* (VI).—α-Naphthylamine (143 g., 1 mol.) was dissolved in hot 20% hydrochloric acid (500 ml.), cooled rapidly, and diazotised with aqueous sodium nitrite (5N.). The diazotised solution was buffered with sodium acetate (300 g.) in water (250 ml.) and then added gradually to a stirred solution of potassium ferrocyanide (928 g., 2 mols.) in water (2 l.). The evolution of nitrogen was immediate and rapid, and it was necessary to add drops of butyl alcohol to prevent foaming. After being left overnight, the brown precipitate was collected, dried (yield, 85%), and extracted for 2 days (Soxhlet) with light petroleum (b. p. 60—80°). The extract was concentrated to 250 ml., and the solid product, which contained much tar, was boiled with benzene, with the addition of charcoal (5 g.). This solution deposited a brown solid which, by successive crystallisations from alcohol, light petroleum (b. p. 60—80°), glacial acetic acid, and finally acetone, gave, in 9% yield, brick-red microscopic needles of 4-α-*naphthyl*-1 : 1′-*azonaphthalene*, m. p. 178° (Found : C, 87·3; H, 4·8; N, 6·9. $C_{30}H_{20}N_2$ requires C, 88·2; H, 4·9; N, 6·9%). This was also synthesised as follows.

4-Nitro-1 : 1′-dinaphthyl (Schoepfle, *loc. cit.*) (10 g.) in boiling alcohol (200 ml.) was treated with a solution of stannous chloride (45 g.) in concentrated hydrochloric acid (40 ml.). After refluxing for 1 hour the alcohol was removed, and the residue poured into 30% sodium hydroxide (300 ml.). The crude 4-*amino*-1 : 1′-*dinaphthyl* was collected, extracted with ether, and finally crystallised from alcohol. It formed pink nodules, m. p. 157—158° (8 g.) (Found : C, 89·3; H, 5·6; N, 5·4. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6; N, 5·2%). Its *acetyl* derivative crystallised from aqueous pyridine in small white plates, m. p. 256·5° (Found : C, 84·4; H, 5·6; N, 4·6. $C_{22}H_{17}ON$ requires C, 84·9; H, 5·6; N, 4·5%), and its *dibenzoyl* derivative had m. p. 210° (Found : C, 85·9; H, 5·2. $C_{34}H_{23}O_2N$ requires C, 85·5; H, 4·9%).

The above base (7 g.) was diazotised in hydrochloric acid suspension. After 20 minutes, excess of nitrous acid was removed with urea (5 g.) and a solution of α-naphthylamine (4 g.) in glacial acetic acid (35 ml.) was added, followed by 30% sodium hydroxide solution (150 ml.). The reddish-brown aminoazo-compound was allowed to settle overnight and then was collected and dried : m. p. ca. 160° (decomp.); yield, quantitative (12 g.). It was dissolved in a mixture of alcohol (100 ml.) and concentrated sulphuric acid (5·4 g.) and treated at 0° with freshly prepared amyl nitrite (3·8 g.). After being kept for 12 hours at room temperature, the mixture was slowly warmed, and finally it was refluxed for an hour. Water was then added, the alcohols were removed under diminished pressure, and the residual black tar was washed with water and extracted with boiling alcohol. The extract, on precipitation with water, gave a bright red solid which was redissolved in 80% alcohol and passed down an alumina column, which retained both tar and azo-dye. The eluted material was repeatedly crystallised from acetone and glacial acetic acid alternately, and finally gave 4-α-naphthyl-1 : 1′-azonaphthalene as dark red granules, m. p. 178—179° not depressed on admixture with the product obtained as before. When crushed, the granules gave a brick-red powder.

Reduction of 4-α-*Naphthyl*-1 : 1′-*azonaphthalene.*—A boiling solution of the azo-compound (10 g.) in glacial acetic acid (200 ml.) was reduced by gradual addition of zinc dust (20 g.), hydrochloric acid (5 ml.) being added to complete the reaction. After filtration, the product was concentrated and treated with a large excess of 50% sodium hydroxide solution; ammonia was then evolved. The resulting solid was collected on sintered glass. No part of it was volatile in steam, and consequently α-naphthylamine was not present. The solid was purified by dissolution in alcohol and partial precipitation with water until a product was obtained which could be recrystallised from benzene–light petroleum (b. p. 40—60°). This was 3-α-*naphthyl*-1 : 2 : 7 : 8-*dibenzcarbazole* (IX), m. p. 218—219°; yield 55% (Found : C, 90·8; H, 4·8; N, 3·4. $C_{30}H_{19}N$ requires C, 91·6; H, 4·9; N, 3·6%). On crystallisation from absolute alcohol it gave brownish-yellow needles of an alcohol complex, which decomposed when heated to 136° to give the free carbazole.

The *picrate* of the carbazole derivative crystallised in maroon-coloured plates, sintering at 246° and melting at 252° (decomp.) (Found : N, 7·9. $C_{36}H_{22}O_7N_4$ requires N, 9·0%).

The carbazole in dilute alcoholic solution showed an intense blue-green fluorescence in ultra-violet light. It gave a pale red solution in concentrated sulphuric acid, which became intense indigo-blue on treatment with many oxidising agents (HNO_3, $K_2Cr_2O_7$, $K_2S_2O_8$, $FeCl_3$, V_2O_5).

Attempted Phenylation of Azobenzene.—Solid zinc benzenediazonium chloride, $(PhN_2Cl)_2,ZnCl_2$, from 18 g. of aniline, was added to a solution of azobenzene (15 g.) in dry acetone (200 ml.) containing suspended calcium carbonate (20 g.), and zinc dust (10 g.) was then added in portions with vigorous shaking. Nitrogen was evolved steadily. On the following day the mixture was heated to boiling and filtered, and the residue was washed with hot acetone. The solution on evaporation gave a brown syrup which was extracted with hot alcohol. From this extract only a brown sludge could be obtained.

Extraction of the latter with light petroleum (b. p. 60—80°), followed by repeated crystallisation, eventually led to the recovery of about 50 mg. of unchanged azobenzene; no other crystalline product could be separated.

Except where otherwise stated, all analyses are by Drs. Strauss and Weiler. M. p.s are uncorrected.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, December 15th, 1949.*]

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169. *The Synthesis of Thyroxine and Related Substances. Part VI. The Preparation of Some Derivatives of* DL-*Thyroxine.*

By J. C. CLAYTON and B. A. HEMS.

A number of new derivatives of DL-thyroxine have been prepared; their solubilities and physiological activities are recorded. A new method of iodination of 3 : 5-di-iodothyronine and its derivatives is described.

IN the introduction to this series (Borrows, Clayton, and Hems, *J.*, 1949, S 185) it was stated that one of the aims of the work was to prepare derivatives of thyroxine that would be suitable for oral administration in the treatment of hypothyroidism. It was generally thought at that time (Harington, " The Thyroid Gland," London, 1933) that free thyroxine was ineffective orally, presumably because of its low solubility and consequent poor absorption from the gut. If that were so a soluble derivative might be more useful. We have prepared certain new derivatives of thyroxine; values have been obtained for their solubilities and physiological potencies, and are shown in the Table. Thyroxine methyl ester is included since no figure for its activity has been reported. The biological activities of these compounds were determined by injection into mice, using the method devised by Smith, Emmens, and Parkes (*J. Endocrinol.*, 1947, **5**, 186).

Substance.	Activity.	Solubility in water, (g./100 ml. at 25°).
DL-Thyroxine monosodium salt	1·0	<0·001 pH 7·0
Thyroxine methyl ester	0·65	0·017 pH 7·6
Thyroxine ethyl ester	0·5	0·002 pH 7·6
N-Formylthyroxine	0·3	0·16 pH 7·3 0·37 pH 9·2
N-Phthaloylthyroxine	inactive	<0·02 pH 7·6
N-*β*-Carboxypropionylthyroxine	0·07	0·95 pH 7·6
N-Oxalothyroxine	0·3	0·14 pH 7·6
O-Carboxymethylthyroxine	0·1	0·03 pH 7·6
N-Carbamylthyroxine sodium salt	inactive	0·6 pH 7·0
Thyroxine methyl ether	0·5	<0·008 pH 7·6

Thyroxine ethyl ester hydrochloride was prepared by treating with hydrogen chloride a suspension of the amino-acid in ethyl alcohol: it was converted into the *ethyl* ester by treatment with the equivalent quantity of sodium hydroxide solution. N-*Formylthyroxine* was prepared by heating the amino-acid with formic acid under reflux, and N-*phthaloylthyroxine* was obtained by treatment of thyroxine with phthalic anhydride at 180° according to Billmann and Harting's general method (*J. Amer. Chem. Soc.*, 1948, **70**, 1473). For other *N*-acyl derivatives the methyl ester of thyroxine in anisole solution was treated with the appropriate acid chloride and the *N*-acyl esters were then hydrolysed with sodium hydroxide solution (cf. Ashley and Harington, *Biochem. J.*, 1928, **22**, 1436). Thus, N-β-*carboxypropionylthyroxine* and N-*oxalothyroxine* were prepared from thyroxine methyl ester and β-carbethoxypropionyl chloride and methoxalyl chloride, respectively.

When thyroxine was heated under reflux with 2N-sodium hydroxide solution and chloroacetic acid, the substance obtained on acidification appeared to be O-*carboxymethylthyroxine*, since it showed a positive ninhydrin reaction, but no colour with sodium nitrite in acid solution followed by basification with ammonia, a test in which 2 : 6-di-iodophenols give a red colour (Kendall and Osterberg, *J. Biol. Chem.*, 1919, **40**, 265; Harington and Barger, *Biochem. J.*, 1927, **21**, 169). Furthermore, electrometric titration demonstrated the presence of one basic group and only two acidic groups.

The monosodium salt of N-*carbamylthyroxine* was prepared by heating the sodium salt of thyroxine with an aqueous solution of sodium cyanate. Attempts to prepare the free hydantoic acid from the sodium salt failed, since rapid cyclisation to *thyroxinehydantoin* took place. This last compound was characterised by catalytic hydrogenolysis, the product proving identical with *thyroninehydantoin* prepared from thyronine by the usual method.

There is some doubt about the activity of thyroxine methyl ether, which has been prepared by two different methods. One was the action of diazomethane on thyroxine, followed by hydrolysis of the resultant ester (Loeser, U.S.P. 2,252,230); the product was reported to melt at 226—228° and was claimed to be highly active. In the other, *N*-acetylthyroxine was methylated with methyl sulphate, and the acetyl group was subsequently removed by hydrolysis (Myers, *Proc. Staff Meetings, Mayo Clinic*, 1932, **7**, 201; *J. Amer. Chem. Soc.*, 1932, **54**, 3718). The product melted at 210—213° and was said to be active when administered to tadpoles, but had no effect upon normal men. Difficulties were encountered in attempting to follow Myers's intructions and no methyl ether was obtained. Consequently, thyroxine methyl ether was prepared by Loeser's procedure and identified as the methyl ether by hydrogenolysis to a compound that proved identical with an authentic specimen of *thyronine methyl ether*; this was prepared by hydrolysis and simultaneous racemisation of 3 : 5-di-iodo-4-*p*-methoxyphenoxy-*N*-acetyl-L-phenylalanine ethyl ester to 3 : *5-di-iodo-*4-p-*methoxyphenoxy-*DL-*phenylalanine*, which was then hydrogenolysed.

In preparing thyroxine by the iodination of 3 : 5-di-iodothyronine in strong aqueous ammonia (Harington and Barger, *loc. cit.*; Harington, *Biochem. J.*, 1928, **22**, 1429) trouble was often encountered through the formation of explosive nitrogen iodides. By careful working, in particular by adding the iodine solution slowly below the surface of the liquid, the formation of nitrogen iodides was avoided, but the method was thought to involve an undesirable risk, particularly in larger scale preparations. To avoid this risk several other known methods of iodination were attempted, but none was satisfactory. Finally it was thought that solutions of organic bases might be useful as solvents, since their iodine derivatives are known to be non-explosive. The use of tertiary bases met with no success, but aqueous or alcoholic solutions of primary or secondary aliphatic bases proved to be very suitable media for iodination. 3 : 5-Di-iodothyronine is much more soluble in these solutions than in aqueous ammonia, and the iodination appeared to proceed more rapidly, although detailed studies on this point have not been carried out. The method is simple and convenient and thyroxine is obtained consistently in 90% yield. Several primary and secondary aliphatic bases have been used and aqueous ethylamine solutions have proved to be generally useful. The method has also been used in the iodination of derivatives of 3 : 5-di-iodothyronine, *N*-formyl- (Harington, *loc. cit.*), N-*acetyl-*, and N-β-*carboxypropionyl-*3 : *5-di-iodothyronine*, giving the corresponding thyroxine derivatives in good yield. Similarly, 3 : *5-di-iodothyroninehydantoin* could be iodinated to thyroxinehydantoin, which proved to be identical with the compound prepared by cyclisation of *N*-carbamylthyroxine.

Although iodination of 3 : 5-di-iodothyronine methyl ester did take place in aqueous solutions of bases, the compound underwent hydrolysis and thyroxine was the sole product. However, under anhydrous conditions, for example, using methyl alcohol and *n*-butylamine as the solvent, thyroxine methyl ester was readily obtained.

EXPERIMENTAL.

Thyroxine Ethyl Ester.—Hydrogen chloride was passed into a mixture of thyroxine (1 g.) and ethyl alcohol (10 ml.), and the solid rapidly went into solution. When the solution was saturated it was allowed to cool and was re-treated with hydrogen chloride. Evaporation yielded a solid residue of the ester hydrochloride (0·97 g.) which was dissolved in aqueous ethyl alcohol; one equivalent of N-sodium hydroxide was then added. The *ethyl* ester was precipitated as a white solid and was filtered off, washed, and dried. It (0·7 g.) had m. p. 156—157° (Found: C, 26·0; H, 1·8; N, 1·75; I, 62·55. $C_{17}H_{15}O_4NI_4$ requires C, 25·4; H, 1·9; N, 1·7; I, 63·1%).

N-*Formylthyroxine.*—Thyroxine (1 g.) was heated under reflux with formic acid (12 ml.; 98—100%) for five hours, and the solution cooled and evaporated *in vacuo* to dryness. The residue was heated for 1·5 hours with more formic acid (10 ml.), and the solution evaporated. The product was completely soluble in dry acetone from which it crystallised on addition of water. The material was recrystallised from aqueous acetone and the N-*formyl* compound separated as a white powder, m. p. 223° (decomp.) (Found: C, 25·2; H, 1·8; N, 1·6; I, 62·0. $C_{16}H_{11}O_5NI_4,\frac{1}{2}C_3H_6O$ requires C, 24·75; H, 1·6; N, 1·7; I, 61·7%).

N-*Phthaloylthyroxine.*—A mixture of thyroxine (0·5 g.) and phthalic anhydride (0·4 g.) was heated in a test-tube to 180°, by means of an oil-bath. The bath was maintained at this temperature for fifteen minutes. The solid slowly melted to a homogeneous brown liquid. After cooling, the solidified mass was extracted with boiling glacial acetic acid, and the solid obtained on cooling was recrystallised from ethyl acetate–light petroleum (b. p. 80—100°) as white prisms (0·3 g.), m. p. 156—157° (decomp.) (Found: C, 30·7; H, 1·8; N, 1·5. $C_{23}H_{13}O_6NI_4$ requires C, 30·45; H, 1·4; N, 1·5%).

N-β-*Carboxypropionylthyroxine.*—To a solution of thyroxine methyl ester (Ashley and Harington, *Biochem. J.*, 1928, **22**, 1436) (1 g.) in anisole (40 ml.) cooled to 0°, a solution of β-carbethoxypropionyl chloride (0·14 g.) (Papa, Schwenk, and Hankin, *J. Amer. Chem. Soc.*, 1947, **69**, 3018) in anisole (2 ml.) was added. After one hour the precipitate was filtered off and identified by m. p. and mixed m. p. as thyroxine methyl ester hydrochloride (0·55 g.). The filtrate was evaporated to dryness *in vacuo* and the residue dissolved in benzene. After a short time white prisms (0·4 g.), m. p. 139—141°, were deposited, and were identified by analysis as N-*β-carbethoxypropionylthyroxine methyl ester* (Found: C, 29·1; H, 2·7; N, 1·4; I, 56·0. $C_{22}H_{21}O_7NI_4$ requires C, 28·7; H, 2·3; N, 1·5; I, 55·3%).

The ester was dissolved in ethyl alcohol (5 ml.) containing N-sodium hydroxide (4 ml.). After one hour at room temperature, N-hydrochloric acid (4 ml.) was added to precipitate the N-*β-carboxypropionylthyroxine*. This crystallised from aqueous alcohol as white prisms (0·25 g.), m. p. 202—203° (decomp.) (Found: C, 25·9; H, 1·5; N, 1·4; I, 57·5. $C_{19}H_{15}O_7NI_4$ requires C, 26·0; H, 1·7; N, 1·6; I, 58·0%).

N-*Oxalothyroxine.*—In a similar manner N-*oxalothyroxine* was prepared from thyroxine methyl ester and methoxalyl chloride; it crystallised from alcoholic alkali, on addition of acetic acid, as a white powder, m. p. 225—226° (decomp.) (Found: C, 24·2; H, 1·7; N, 1·6; I, 62·4. $C_{17}H_{11}O_7NI_4$ requires C, 24·05; H, 1·3; N, 1·65; I, 59·8%).

O-*Carboxymethylthyroxine.*—To thyroxine (1 g.) in water (30 ml.) containing N-sodium hydroxide (6 ml.) chloroacetic acid (0·12 g.) was added, and the mixture was boiled under reflux for two hours. An equal volume of alcohol was added and the mixture was treated with charcoal and filtered, and the pH adjusted to 5 by addition of glacial acetic acid. On cooling, silvery plates were deposited which were recrystallised by solution in alcoholic alkali and addition of acetic acid. O-*Carboxymethylthyroxine* (0·7 g.) had m. p. 208—209° (decomp.) (Found: C, 24·2; H, 2·1; N, 1·6; I, 60·1. $C_{17}H_{13}O_6NI_4$ requires C, 24·4; H, 1·6; N, 1·7; I, 60·9%).

Sodium Salt of N-*Carbamylthyroxine.*—Thyroxine monosodium salt (1 g.) suspended in water (75 ml.) containing sodium cyanate (0·4 g.) was heated under reflux for one hour and then an aqueous solution (25 ml.) of sodium cyanate (0·4 g.) was added and heating continued for three hours. The clear solution was concentrated *in vacuo* to 50 ml. and kept in the ice-chest whereupon the *sodium* salt separated as a white powder (0·7 g.). It was purified by dissolution in methyl alcohol (10 ml.) and addition of ether (100 ml.) whereupon a white solid was obtained (Found: N, 3·3; I, 59·5; Na, 2·9. $C_{16}H_{11}O_5N_2I_4Na$ requires, N, 3·3; I, 60·3; Na, 2·7%).

5-[3 : 5-*Di-iodo*-4-(3 : 5-*di-iodo-4-hydroxyphenoxy*)*benzyl*]*hydantoin.*—To a suspension of thyroxine monosodium salt (0·8 g.) in water (75 ml.) 0·2N-sodium hydroxide (8 ml.) and sodium cyanate (0·4 g.) were added and the solution was heated under reflux for 2·5 hours. Concentrated hydrochloric acid (40 ml.) was added, and heating was continued for one hour. After cooling, the *hydantoin* was filtered off and recrystallised from acetic acid from which it separated as white prisms (0·73 g.), softening at 169—170° and decomposing at 235° (Found: C, 25·4; H, 1·6; N, 3·4. $C_{16}H_{10}O_4N_2I_4,C_2H_4O_2$ requires C, 25·1; H, 1·6; N, 3·25%).

5-(4-p-*Hydroxyphenoxybenzyl*)*hydantoin.*—(*a*) A suspension of thyronine (2 g.) in water (20 ml.) containing sodium cyanate (1 g.) was refluxed until all solid had dissolved. Concentrated hydrochloric acid (12 ml.) was added and the mixture was heated under reflux for a further 30 minutes. The solid obtained on cooling was filtered off and recrystallised from aqueous acetic acid from which the *hydantoin* separated as colourless feathery clusters (1·9 g.), m. p. 256—257° (decomp.) (Found: C, 64·0; H, 4·8; N, 9·3. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7; N, 9·4%).

(*b*) 5-[3 : 5-Di-iodo-4-(3 : 5-di-iodo-4-hydroxyphenoxy)benzyl]hydantoin (0·17 g.) was hydrogenolysed in 0·1N-sodium hydroxide solution (20 ml.) using palladised calcium carbonate (0·5 g.) as catalyst. The crude product was crystallised from aqueous acetic acid and proved identical [m. p. and mixed m. p. 256—257° (decomp.)] with a specimen of the material obtained in (*a*) above (yield, 0·055 g.).

Thyroxine Methyl Ether.—This compound was prepared from thyroxine methyl ester by treatment with diazomethane and hydrolysis (Loeser, U.S.P. 2,252,230). It had m. p. 224—225° (decomp.).

3 : 5-*Di-iodo*-4-p-*methoxyphenoxy*-DL-*phenylalanine.*—A mixture of 3 : 5-di-iodo-4-*p*-methoxyphenoxy-*N*-acetyl-L-phenylalanine ethyl ester (see Part V, *J.*, 1949, 3424) (2 g.) and 2N-sodium hydroxide solution (30 ml.) was heated under reflux for 24 hours. To the cooled solution, acetic acid was added whereupon a white solid was deposited. This was filtered off and recrystallised from 50% aqueous acetic acid, from which the *phenylalanine* separated as white prisms, m. p. 238—239° (decomp.) (Found: N, 2·3; I, 46·9. $C_{16}H_{15}O_4NI_2$ requires N, 2·6; I, 47·1%).

Thyronine Methyl Ether.—(*a*) A solution of 3 : 5-di-iodo-4-*p*-methoxyphenoxyphenylalanine (0·6 g.) in ethyl alcohol (10 ml.) and 2N-sodium hydroxide (10 ml.) was shaken in hydrogen with palladised calcium carbonate (0·5 g.) until the uptake of hydrogen was complete. The filtered solution was acidified with acetic acid and, on storage, colourless needles of *thyronine methyl ether* separated and were crystallised from aqueous ethyl alcohol. This ether had m. p. 248° (decomp.) (Found: C, 66·8; H, 6·2; N, 5·0. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%).

(*b*) A solution of thyroxine methyl ether (0·4 g.) in ethyl alcohol (8 ml.) and 2N-sodium hydroxide (8 ml.) was shaken in hydrogen with palladised calcium carbonate (0·5 g.) until hydrogenolysis was complete. The solution was filtered and acidified with acetic acid; a white solid, m. p. 246° (decomp.) undepressed on admixture with a sample of thyronine methyl ether from (*a*) above, was precipitated.

Iodination of 3 : 5-*Di-iodothyronine and Its Derivatives.*—*Thyroxine.* To a stirred solution of 3 : 5-di-iodothyronine (2 g.) in aqueous ethylamine solution (20 ml.; 20%) a solution of iodine in potassium iodide solution (8·2 ml.; 1·85N.) was added dropwise. After being stirred for ten minutes the mixture was acidified with glacial acetic acid, and the precipitated thyroxine was filtered off and redissolved in ethyl alcohol (20 ml.) and 2N-sodium hydroxide solution (10 ml.). The hot solution was acidified with acetic acid; the thyroxine separated as a microcrystalline powder (2·6 g.; 90%), m. p. 231—232° (decomp.).

3 : 5-*Di-iodo*-N-*acetylthyronine*. To a solution of 3 : 5-di-iodothyronine methyl ester (1 g.) in anisole (30 ml.), a solution of acetyl chloride (0·072 g.) in anisole (2 ml.) was added. Later the precipitate was filtered off and identified by m. p. and mixed m. p. [227° (decomp.)], as 3 : 5-di-iodothyronine methyl ester hydrochloride (0·54 g.). The filtrate was evaporated to dryness *in vacuo* and the residue was

dissolved in ethyl alcohol (5 ml.) and N-sodium hydroxide (5 ml.). After one hour N-hydrochloric acid (5 ml.) and water (30 ml.) were added to precipitate a white solid which was recrystallised from glacial acetic acid. It formed white prisms, m. p. 207—208° (0·35 g.) (Found: C, 36·0; H, 2·65; N, 2·2; I, 44·8. $C_{17}H_{15}O_5NI_2$ requires C, 36·0; H, 2·7; N, 2·5; I, 44·8%).

3 : *5-Di-iodo-*N*-β-carboxypropionylthyronine.* To a solution of 3 : 5-di-iodothyronine methyl ester (1 g.) in anisole (20 ml.) a solution of β-carbethoxypropionyl chloride (0·07 g.) in anisole (2 ml.) was added. The precipitated 3 : 5-di-iodothyronine methyl ester hydrochloride was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in ethyl alcohol (5 ml.) and N-sodium hydroxide (5 ml.). After one hour N-hydrochloric acid (5 ml.) was added and the solid filtered off. It was dissolved in alcoholic alkali, treated with charcoal, and reprecipitated with acid to give tiny white prisms of 3 : *5-di-iodo-*N*-β-carboxypropionylthyronine* (0·3 g.), m. p. 231—232° (decomp.) (Found: N, 2·2; I, 41·2. $C_{19}H_{17}O_7NI_2$ requires N, 2·2; I, 40·7%).

Using the above method of iodination *N*-formyl-, *N*-acetyl-, and *N*-β-carboxypropionyl-thyroxine and 5-[3 : 5-di-iodo-4-(3 : 5-di-iodo-4-hydroxyphenoxy)benzyl]hydantoin were prepared from the corresponding derivatives of 3 : 5-di-iodothyronine and 5-(3 : 5-di-iodo-4-*p*-hydroxyphenoxybenzyl)-hydantoin.

Thyroxine methyl ester. To a solution of 3 : 5-di-iodothyronine methyl ester (1 g.) in *n*-butylamine (10 ml.) and methyl alcohol (20 ml.) a solution of iodine (1 g.) in methyl alcohol (10 ml.) was added. After one hour methanolic hydrogen chloride was added until the reaction solution was acid; dilution with water containing a little sodium acetate precipitated the crude ester which was extracted with methyl alcohol to give the pure compound (0·7 g.), m. p. and mixed m. p. 158°.

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Research Division, Glaxo Laboratories, Ltd.,
Greenford, Middlesex.

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170. *Studies in Co-ordination Chemistry. Part I. Complexes of Quadrivalent Platinum with Tertiary Arsines.*

R. S. Nyholm.

A series of octahedral complexes of quadrivalent platinum which have the general formula $Pt(Hal)_4,2AsR_3$ have been prepared by using various halides and tertiary arsines. They are all very stable compounds which are difficult to reduce. The complexes are more deeply coloured than their bivalent, planar analogues and are less soluble than these in organic solvents. Differences in reactivity between *cis*- and *trans*-isomers of these octahedral complexes similar to those shown by the bivalent square complexes have been observed. The properties of the compounds are discussed.

This paper is the first of a series dealing with the complexes of metal salts with tertiary arsines. It is proposed to investigate the properties of these complexes as a function of the valency state of the metal and of the anion present and to attempt the preparation of halogen-bridged complexes. Initially the investigation is confined to the elements of Group VIII. Tertiary arsines and phosphines show many properties as ligands which distinguish them from ammonia and amines; they have a very marked tendency to form non-ionic complexes which are freely soluble in organic solvents rather than salt-like substances which are formed so readily by ammonia. It is thus possible to apply a variety of techniques to the study of these compounds which cannot be used with ammines because of their insolubility in organic solvents. A detailed discussion of these differences and an attempt to explain them with particular reference to the nature of the metal–arsenic bond will be given in a later communication. However, the complexes of the elements in many of their valency states with tertiary arsines have not been investigated, and as a first step the preparation of these and a study of their properties were considered desirable.

Tertiary arsines have been used frequently for the stabilisation of lower-valency states, for which purposes their reducing properties are an advantage. In higher-valency states, however, any tendency towards dissociation of the complex might be expected to lead to decomposition, since the compound contains both an oxidising and a reducing agent combined. For instance, Mann and Purdie (*J.*, 1940, 1235) observed that several of the complexes of tervalent gold with triethylphosphine were unstable on standing; triethylphosphinetrichlorogold(III), $[AuCl_3,PEt_3]$, for example, decomposed within a few days on standing at room temperature, even when kept in the dark, metallic gold being deposited. The tri-iodide decomposed within a few weeks but the tribromide was stable indefinitely. Although tertiary phosphines are as a rule stronger ligands than tertiary arsines, they are similar to them in many ways; thus both tend to form non-ionic complexes with metal salts of the same general type and both are strong reducing agents.

No complexes of quadrivalent platinum with tertiary arsines have been described previously. Of similar complexes with tertiary phosphines, Cahours and Gal (*Compt. rend.*, 1870, **70**, 902) mentioned two platinic complexes with triethylphosphine but no analyses were given. Also, Rosenheim and Lowenstamm (*Z. anorg. Chem.*, 1903, **37**, 400) prepared the compound $PtCl_4,2P(OC_2H_5)_3$ but no analyses were reported.

All the platinic complexes described in this paper have the general formula $Pt(Hal)_4,2AsR_3$, and where solubilities permitted the determination of molecular weights in freezing benzene or freezing bromoform they were monomeric. All were prepared by adding the appropriate amount of the required halogen dissolved in carbon tetrachloride to the planar four-covalent complex of bivalent platinum dissolved in chloroform or benzene. The solvent used was very important in many cases, for the chloride complexes were often obtained as difficultly crystallisable oils from solvents other than benzene. Complexes of triethyl-, triphenyl-, and diphenylmethylarsine have been studied; the last has been found convenient for many other Group VIII metals but on occasions it led to the formation of isomeric mixtures. In all cases the platinic complexes were less soluble in organic solvents than the corresponding bivalent compounds from which they were derived. As with the bivalent complexes, solubility of the *cis*-bisarsine compounds was much less than that of the corresponding *trans*-isomers. For any given isomer the solubility decreased in the sequence chloride > bromide > iodide. As expected, the solubility of the bistriethylarsine complexes was much greater than that of the triphenyl or mixed aryl–alkyl derivatives.

The complexes were all highly coloured, the colour deepening in passing from the bivalent to the quadrivalent state and also in passing from the chloride through the bromide to the iodide. Where obtained, the *cis*-isomers were lighter in colour than the *trans*-isomers. The properties of a typical series are shown in the table

			Bivalent compounds.	
Platinic complex.	Colour.	M. p.	Colour.	M. p.
cis-$PtCl_4,2AsEt_3$	Pale yellow	125°	White	142°
trans-$PtCl_4,2AsEt_3$	Dark yellow	155	Yellow	120
trans-$PtBr_4,2AsEt_3$	Scarlet	173	Deep yellow	120
trans-$PtI_4,2AsEt_3$	Purplish-black	144	Orange	94

Probably the most noteworthy property of the complexes was their stability on standing and towards reducing agents. Only with the *cis*- and the *trans*-form of the *chloride* $PtCl_4,2AsEt_3$ was instability on standing observed; these two substances became oily after several months but the corresponding *tetrabromide* and *tetraiodide* were stable indefinitely Complexes of the other arsines showed no sign of decomposition after several months. On heating, the complexes melted without decomposition as a rule, in some cases above 200°. Unlike the triethylphosphine–gold complexes, they could be boiled with alcohol or acetone without reduction taking place. Sulphur dioxide similarly did not cause reduction except in one or two cases. Thus, although the *compounds* $PtCl_4,2AsMePh_2$ and $PtI_4,AsMePh_2$ were not reduced by sulphur dioxide in chloroform solution, the *complex* *trans*-$PtCl_2I_2,2AsMePh_2$ was reduced in ½ hour by this means; the product was *trans*-$PtI_2,2AsMePh_2$, the more electronegative halogen being removed. On the other hand, if one attempted to reduce the *cis*-dichloro-*trans*-di-iodo-compound, disproportionation to form the tetrachloro- and tetraiodo-compounds occurred without reduction taking place. Throughout the investigation it was observed that the mixed halogen compounds disproportionated very easily.

Towards most chemical reagents the *trans*-compounds were less reactive than the corresponding *cis*-isomers. For instance, an alcoholic solution of *cis*-$PtCl_4,2AsEt_3$ reacted instantly with aqueous silver nitrate but the corresponding *trans*-complex gave no precipitate for some hours. Similarly, the *cis*-compound reacted vigorously with concentrated sulphuric acid, an effervescence occurring with the evolution of hydrogen chloride; the *trans*-compound dissolved to an orange solution which slowly charred. This difference in reactivity is similar to that observed for the *cis*- and *trans*-planar complexes of bivalent platinum.

Some interesting facts on *cis*–*trans*-isomerism were noticed. Jensen (*Z. anorg. Chem.*, 1936, **229**, 225) observed that stability of *cis*-isomers of the type $Pt(Hal)_2,2AsEt_3$ increased in passing from the iodide to the chloride; the *cis*-di-iodo-complexes had to be made indirectly and soon reverted to the *trans*-forms on heating. This behaviour has also been observed with the diphenylmethylarsine anologues; the iodide forms a complex which is readily soluble in benzene and is undoubtedly the *trans*-form, but the much less soluble *cis*-form is favoured by the chloride and bromide. The equilibrium between *cis*- and *trans*-forms appeared to be much affected by both solvent and temperature in the cases of the chloride and bromide, which made the preparation of pure isomers difficult. The tetrabromo- and tetrachloro-platinum complexes of this arsine favoured the *cis*-form. An interesting difference was observed between the stabilities of the *cis*- and the *trans*-form of $PtCl_2,2AsEt_3$ and the corresponding tetrachlorides. The white *cis*-platinous complex required heating in solution for many days to convert it into the more soluble, yellow *trans*-isomer. However, the corresponding *cis*-tetrachloro-complex formed a considerable amount of the darker yellow *trans*-isomer on being left in the sunlight for a few hours. In these circumstances the *cis*-platinous complex was stable indefinitely. It appears to be well established that the stability of the *cis*-forms, both of bivalent and of quadrivalent platinum, increases with increasing electronegativity of the attached halogen, but steric factors depending on the particular arsine used are also important.

As expected for octahedrally co-ordinated quadrivalent complexes using d^2sp^3 bonds, the complexes are diamagnetic and the specific susceptibility of the compound $PtBr_4,2AsMePh_2$ ($\chi = -0{\cdot}41 \times 10^{-6}$) is of the order found by Asmussen (Doctorial Thesis, Copenhagen, 1941) for a large number of quadrivalent platinum complexes.

Apart from two complexes involving the $[PtCl_6]^{2-}$ ion, no salt-like complexes with tertiary arsines were isolated, and all attempts to obtain tertiary arsine complexes corresponding to ammines such as $[Pt(NH_3)_5Cl]Cl_3$ or $[Pt(NH_3)_4Cl_2]Cl_2$ were unsuccessful. Also, no halogen-bridged quadrivalent complexes were isolated. It is concluded from a study of these very stable complexes that combination of a tertiary arsine with a metal in a high oxidation state does not lead to instability provided that strong covalent bonds are formed between the metal and the arsenic atom.

EXPERIMENTAL.

Complexes of Triethylarsine.—*Bivalent compounds.* These were all prepared by Jensen's method (*Z. anorg. Chem.*, 1936, **229**, 225). The colour and m. p.s (Jensen's m. p.s in parentheses) were: *cis*-$PtCl_2,2AsEt_3$, white, m. p. 142° (142—142·5°); *trans*-$PtCl_2,2AsEt_3$, yellow, m. p. 119° (120—121°); *trans*-$PtBr_2,2AsEt_3$, deep yellow, m. p. 120° (120—121°); *trans*-$PtI_2,2AsEt_3$, orange, m. p. 92° (94°). The yield of *trans*-$PtCl_2,2AsEt_3$ was very much smaller than that of the *cis*-isomer produced simultaneously. The *cis*- was converted into the *trans*-form by refluxing in chloroform solution for several days, the isomerisation being very slow.

Jensen (*loc. cit.*) assigned the *cis*- and *trans*-configurations to the above compounds on the basis of their electric dipole moments in benzene, that of the *trans*-forms being zero and that of the *cis*- being in the vicinity of 10 Debye units. He pointed out that the *trans*-isomers differed from the *cis*- in several of their physical properties, and foremost amongst these were their colours and solubilities in benzene. The *trans*-forms were deeper in colour and were much more soluble in benzene than the *cis*-isomers. Special consideration has been given to these properties in the assignment of the *cis*- or *trans*-configuration to the various platinous complexes described here.

Bistriethylarsinetetrachloroplatinum(IV). (i) *trans*-Isomer. *trans*-Bistriethylarsinedichloroplatinum(II) (1·1 g.), dissolved in cold chloroform (25 ml.), was treated with gaseous chlorine until no further absorption occurred. The solution became warm and changed colour from deep yellow to orange red. The chloroform was then removed at the pump at room temperature, and the orange residue recrystallised from alcohol. The *compound* was obtained as short, stumpy, dark yellow crystals, m. p. 155° (Found: C, 21·7; H, 4·6; Pt, 19·5; *M*, cryoscopic in 2·58% solution in benzene, 630. $C_{12}H_{30}Cl_4As_2Pt$ requires C, 21·75; H, 4·5; Pt, 19·6%; *M*, 661). It dissolved readily in benzene and other organic solvents except light petroleum. An acetone solution gave no reaction with silver nitrate unless heated and left for some time. After many months' standing the compound became oily.

(ii) *cis*-Isomer. *cis*-Bistriethylarsinedichloroplatinum(II) (1·2 g.), dissolved in chloroform (15 ml.), was treated with gaseous chlorine as above, the solution becoming warm and acquiring a bright yellow colour. After removal of the chloroform at room temperature at the pump, the yellow residue was recrystallised from alcohol. The *compound* was obtained as yellow needles which formed a characteristic mat; it was much lighter in colour than the *trans*-isomer and melted at 125° (Found: C, 21·9; H, 4·7; Pt, 19·5%). It was moderately soluble in alcohol and acetone but practically insoluble in benzene even when boiling. If heated under reflux for a long time with benzene it gradually dissolved to a yellow solution of the *trans*-isomer. This change also occurred on standing in sunlight, a behaviour in marked contrast with that of the bivalent *cis*-compound which on standing shows no tendency at all to change into the *trans*-isomer. An acetone solution gives an immediate copious precipitate with silver nitrate solution, a reaction in which it differs from the *trans*-isomer. When treated with concentrated sulphuric acid, the *cis*-isomer reacted immediately with effervescence with the evolution of hydrogen chloride; when similarly treated, the *trans*-isomer dissolved to an orange solution and slow charring then took place.

trans-*Bistriethylarsinetetrabromoplatinum*(IV). *trans*-Bistriethylarsinedibromoplatinum(II) (1·40 g.), dissolved in benzene (15 ml.) (yellow solution), was treated with bromine (0·34 g.) in carbon tetrachloride (4 ml.) and the solution immediately became deep red. Evaporation at the pump at ordinary temperatures yielded beautiful scarlet crystals m. p. 172° raised by recrystallisation from alcohol to 173°. The *compound* crystallised as flat rhombs (Found: Pt, 23·2; *M*, cryoscopic in 1·33% solution in benzene, 775. $C_{12}H_{30}Br_4As_2Pt$ requires Pt, 23·3%; *M*, 839). It dissolved readily in organic solvents, particularly benzene and chloroform. An acetone solution slowly precipitated silver chloride on treatment with silver nitrate.

trans-*Bistriethylarsinetetraiodoplatinum*(IV).—*trans*-Bistriethylarsinedi-iodoplatinum(II) (1·2 g.), dissolved in chloroform (30 ml.), was treated with iodine (0·4 g.) dissolved in chloroform (40 ml.), the light orange solution turning to a dark wine-red colour. After evaporation of the chloroform at the pump, the residue was recrystallised from alcohol. The *compound* was obtained as purplish black, flat rectangular crystals, m. p. 144° (Found: Pt, 18·9. $C_{12}H_{30}I_4As_2Pt$ requires Pt, 19·0%); it was readily soluble in benzene and chloroform to a red solution but less soluble than either the chloride or the bromide.

Complexes of Triphenylarsine.—*cis*-Bistriphenylarsinedichloroplatinum (II) was prepared according to Jensen (*loc. cit.*). It decomposed above 300° on heating (Found: Pt, 22·0. Calc. for $C_{36}H_{30}Cl_2As_2Pt$: Pt, 22·0%).

trans-Bistriphenylarsinedichloroplatinum(II) was prepared from the *cis*-isomer by Jensen's method (*loc. cit.*). He recommended refluxing in chloroform for 15 minutes, but in this experiment the *cis*-isomer (0·65 g.) was refluxed with chloroform (36 ml.) for 1½ hours, the almost colourless solution turning deep yellow. Removal of the chloroform gave a compound slightly more yellow than the starting material. This was dissolved in benzene (50 ml.) by refluxing, cooled, and treated with chlorine (0·05 g.) in carbon tetrachloride (2 ml.). The solution became bright yellow and on concentration it afforded yellow crystals which can be recrystallised from benzene with difficulty in small quantities; m. p. 290° (Found: Pt, 20·7. $C_{36}H_{30}Cl_4As_2Pt$ requires Pt, 20·6%). Owing to the low solubility of complexes of this *tetrachloroarsine*, no other complexes were prepared.

Complexes of Diphenylmethyarsine.—*Bisdiphenylmethylarsinedichloroplatinum*(II). This compound was isolated in two forms; one is an almost white, crystalline substance, m. p. 223°, practically insoluble in organic solvents, and the other is light yellow and slightly more soluble, and on heating softens first at 207° and then melts at 214°. On standing or heating, the form of m. p. 214° changes over into that of m. p. 223°, which is no doubt the *cis*-isomer. Unfortunately, low solubility in cold benzene prevented confirmation of this by electric-dipole measurements. Burrows and Parker (*J. Proc. Roy. Soc. N.S.W.*, 1934, **68**, 39) obtained these compounds, one as yellow prisms, m. p. 207° readily soluble in toluene, and the other as yellow needles, m. p. 218°, much less soluble in toluene.

Low-melting form. Diphenylmethylarsine (1·5 g.), dissolved in alcohol (50 ml.), was added to hexahydrated chloroplatinic acid (1·0 g.) dissolved in alcohol (150 ml.), and the solution heated on the water-bath for one hour. Yellow crystals began to form, and on cooling an almost quantitative yield (1·4 g.) was obtained (Found: C, 41·3; H, 3·4; Cl, 9·3; Pt, 25·9. Calc. for $C_{26}H_{26}Cl_2As_2Pt$: C, 41·3; H, 3·4; Cl, 9·4; Pt, 25·8%). The compound was washed many times with alcohol, recrystallisation being difficult without change into the other form taking place. It was readily soluble in chloroform, fairly soluble in acetone but less soluble in cold benzene, from which it crystallised as the other form.

High-melting form. This preparation is commenced as for the other isomer but more concentrated solutions are used. Diphenylmethylarsine (7 g.), dissolved in alcohol (250 ml.), was added to hexahydrated hexachloroplatinic acid (5 g.) dissolved in alcohol (250 ml.). After a few seconds' heating an orange-yellow precipitate appeared which decomposed on further heating, forming a yellow, horny mass and a white powder. The mixture was heated for about an hour, the mass being occasionally broken up, and was then filtered and the residue extracted with chloroform. Removal of chloroform from the almost colourless solution gave a white compound, m. p. 223°, which was less soluble than the other isomer in all solvents (Found: C, 41·4; H, 3·5; Pt, 25·8%).

Two by-products were isolated during a study of the above reaction. When the arsine and chloroplatinic acid reacted in cold alcoholic solution, a yellow precipitate was obtained after about 20 seconds. This substance was insoluble in all solvents, and heating caused decomposition in all solvents tried. The composition varied slightly (C, 39·2—39·8; H, 3·0—3·4; Cl, 13·6; Pt, 23·9—24·7%), but agreed fairly well with $[Pt(AsMePh_2)_4][PtCl_6]$ which requires C, 39·5; H, 3·29; Cl, 13·65; Pt, 24·75%. Its insolubility supports the above formulation and it may be similar to salts of the type $[Pt(AsR_3)_4][PtCl_4]$ isolated by Jensen using trialkylarsines. It is suggested that the platinichloride, rather than the platinochloride, was formed here because reduction with diphenylmethylarsine proceeds more slowly than with trialkylarsines and the temporary co-existence of $[Pt(AsR_3)_4]^{2+}$ and $[PtCl_6]^{2-}$ ions is feasible. From the filtrate of this preparation large orange crystals were obtained after standing for 24 hours. These had m. p. 224° (decomp.) and were insoluble in all solvents. The compound was decomposed by heating with dilute sodium hydroxide solution. The analysis (Found: C, 34·4; H, 3·1; Cl, 23·8; Pt, 21·2%) suggests a formulation as the *salt* $[HAsMePh_2]_2[PtCl_6]$, which requires C, 34·7; H, 3·12; Cl, 23·7; Pt, 21·7%. This substance appears to be one of the few cases where addition of a proton to a tertiary arsine takes place.

Bisdiphenylmethylarsinedibromoplatinum(II).—Diphenylmethylarsine (1·5 g.), dissolved in alcohol (125 ml.), was added to a solution of sodium bromide (5 g.) in distilled water (25 ml.), and the solution added to hexahydrated chloroplatinic acid (1·0 g.) dissolved in alcohol (25 ml.). The buff-coloured precipitate first formed gradually dissolved on heating on the water-bath and the solution lightened in colour. The bright yellow crystals which were slowly precipitated were filtered off after about 2 hours and well washed with alcohol. After recrystallisation from acetone the compound melted at 201° (Found: C, 37·5; H, 3·1; Pt, 23·1. Calc. for $C_{26}H_{26}Br_2As_2Pt$: C, 37·0; H, 3·1; Pt, 23·1%). Burrows and Parker (*loc. cit.*) first described this compound and reported m. p. 196°. It is only very slightly soluble in cold benzene but dissolves on heating; the low solubility in benzene in comparison with that of the iodide indicates that the compound is almost certainly the *cis*-form.

Bisdiphenylmethylarsinedi-iodoplatinum(II).—Diphenylmethylarsine (1·5 g.) and potassium iodide (5 g.), dissolved in a mixture of water (30 ml.) and alcohol (150 ml.), were added to hexahydrated hexachloroplatinic acid (1·0 g.) dissolved in alcohol (20 ml.). The pale pink precipitate which formed at once gradually darkened on heating on the water-bath and after about 3 hours was replaced by a pinkish-orange crystalline powder in a colourless solution. This precipitate was then filtered off, washed many times with alcohol, and recrystallised from benzene and light petroleum; m. p. 229° (Found: C, 33·3; H, 2·8; Pt, 20·6. $C_{26}H_{26}I_2As_2Pt$ requires C, 33·3; H, 2·8; Pt, 20·8%). The *compound* dissolved very readily in chloroform and cold benzene and was fairly soluble in acetone. From its ready solubility in benzene it is undoubtedly the *trans*-isomer.

Bisdiphenylmethylarsinetetrachloroplatinum(IV). This *compound* had to be prepared in benzene solution for it was obtained from chloroform–carbon tetrachloride as a low-melting, difficultly crystallisable substance containing solvent which was very difficult to remove. Bisdiphenylmethylarsinedichloroplatinum (II) (m. p. 223°) (0·75 g.) was dissolved in benzene (75 ml.) by heating under reflux, and chlorine (0·075 g.) in carbon tetrachloride (10 ml.) was added to the warm solution. The light yellow solution deepened in colour and after removal of about half of the solvent the compound crystallised as deep yellow microcrystalline rods (0·6 g.) which were filtered off and washed with benzene, in which they are only very slightly soluble. It may be recrystallised from benzene, the m. p. varying from 205° to 215°, the lower m. p. form gradually increasing on standing (Found, for form of m. p. 205° : C, 37·4; H, 3·1; Pt, 23·9. Found, for form of m. p. 215° : C, 37·8; H, 3·1; Cl, 17·3; Pt, 23·7. $C_{26}H_{26}Cl_4As_2Pt$ requires C, 37·8; H, 3·1; Cl, 17·4; Pt, 23·7%). The substance appears to be an equilibrium mixture of *cis*- and *trans*-forms, but attempts to separate them were not successful. Owing to the low solubility even in bromoform the molecular weight could not be determined.

Bisdiphenylmethylarsinetetrabromoplatinum(IV). Bisdiphenylmethylarsinedibromoplatinum(II) (m. p. 201°) (3·05 g.), dissolved in chloroform (35 ml.), was treated with bromine (0·58 g.) dissolved in carbon tetrachloride (9 ml.) at room temperature. The yellow solution immediately became orange-red in colour and was concentrated at room temperature at the pump to about 10 ml. Orange crystals of the *tetrabromo*-compound (3·1 g.) crystallised out, and were recrystallised from chloroform–carbon tetrachloride. The m. p. varied from 212° to 218°, but after standing for some weeks the compound melted at 214° (Found: C, 31·5; H, 2·7; Pt, 19·3%). The first preparation melted at 227° (Found: C, 30·6; H, 2·9; Br, 31·9; Pt, 19·1%; *M*, cryoscopic in 0·737% solution in bromoform, 967. $C_{26}H_{26}Br_4As_2Pt$ requires C, 31·1; H, 2·6; Br, 31·9; Pt, 19·4%; *M*, 1003) and was more soluble in organic solvents, but heating, recrystallisation, or standing caused a gradual fall in the m. p. to that of the less soluble form. The compound (m. p. 214°) is soluble in chloroform, slightly soluble in benzene, but practically insoluble in alcohol or acetone, and is quite insoluble in ether or light petroleum; it is too insoluble both in freezing bromoform and in boiling benzene for the molecular weight to be determined.

The form of m. p. 227° is probably *trans*-, and the other an equilibrium mixture of *cis*- and *trans*-isomers.

Bisdiphenylmethylarsinetetraiodoplatinum(IV). Bisdiphenylmethylarsinedi-iodoplatinum(II) (*trans*) (1·76 g.), dissolved in chloroform (25 ml.), was treated with iodine (0·45 g.) dissolved in chloroform–carbon tetrachloride (10 ml.; 1 : 1). After a few seconds the light orange solution became dark wine-red in colour and glistening purplish-black crystals were precipitated. The solution was concentrated to about 15 ml. at room temperatures at the pump, and a yield of 1·9 g. of the *tetraiodide* was obtained which melted at 193° after recrystallisation from chloroform and carbon tetrachloride. The compound is fairly soluble in chloroform and bromoform but not very soluble in benzene. Its properties indicate that it is the *trans*-isomer (Found: C, 25·8; H, 2·4; I, 42·6; Pt, 16·2%; *M*, cryoscopic in 0·507% solution in bromoform, 1100. $C_{26}H_{26}I_4As_2Pt$ requires C, 26·2; H, 2·2; I, 42·8; Pt, 16·4%; *M*, 1191).

Bisdiphenylmethylarsinedichlorodibromoplatinum(IV). Oxidation of *cis*-$PtCl_2,2AsMePh_2$ with bromine or of *cis*-$PtBr_2,2AsMePh_2$ with chlorine gave the same product (m. p. and mixed m. p.): it may be an equilibrium mixture.

The dibromo-compound (m. p. 201°) (0·84 g.) in chloroform (25 ml.) was treated with chlorine (0·071 g.) in carbon tetrachloride (5 ml.) and the yellow solution turned orange. Carbon tetrachloride (10 ml.) was added, and the solution concentrated to half bulk, filtered from a small amount of sticky material, and then evaporated to dryness, and the residue was recrystallised from carbon tetrachloride–chloroform. The *compound* was obtained as a microcrystalline powder, m. p. 203° (Found: C, 34·3; H, 2·9; Pt, 21·1. $C_{26}H_{26}Cl_2Br_2As_2Pt$ requires C, 34·1; H, 2·8; Pt, 21·3%). It was also prepared by the action of bromine (0·09 g.) in carbon tetrachloride (1·5 ml.) on the chloro-compound (m. p. 223°) (0·4 g.) dissolved in benzene (60 ml.) by heating. After evaporation of the bulk of the solvent, the orange complex was obtained; m. p. 203°. Solubilities are low, suggesting that the two arsine groups are *cis*-, but the configuration of the halogens is unknown.

Bisdiphenylmethylarsinedichlorodi-iodoplatinum(IV). This compound was prepared by two methods. (*a*) Bisdiphenylmethylarsinedi-iodoplatinum(II) (m. p. 229°, *trans*-) (1·9 g.) was dissolved in chloroform (30 ml.), and chlorine (0·142 g.) in carbon tetrachloride (10 ml.) added. The solution was kept cold and changed colour from pink to dark wine-red. Concentration at the pump at room temperature precipitated a brownish powder, m. p. 163°. The compound crystallised as brown rods; it was not recrystallised for fear of disproportionation.

(*b*) Bisdiphenylmethylarsinedichloroplatinum(II) (m. p. 214°) (0·75 g.) was dissolved in cold chloroform (30 ml.), and iodine (0·25 g.) in carbon tetrachloride–chloroform (10 ml.; 1 : 1) added The very pale yellow turned to a dark red colour, and evaporation at room temperature at the pump to a volume of 10 ml. precipitated light brown crystals of the required complex, m. p. 163° (Found: C, 31·2; H, 2·6; Pt, 19·3. $C_{26}H_{26}Cl_2I_2As_2Pt$ requires C, 30·9; H, 2·6; Pt, 19·3%).

From its method of preparation this compound is clearly a trans-*dichloro*-trans-*di-iodobisarsine* complex. Attempts to obtain an analytically pure specimen of the *cis*-dichloro-*trans*-di-iodo-complex were unsuccessful because disproportionation occurred so rapidly that the first fraction crystallising from the reaction mixture was contaminated with the tetraiodo-compound.

Reduction of Bisdiphenylmethylarsinedichlorodi-iodoplatinum(IV). The above *trans*-compound (0·5 g.), freshly prepared by the action of chlorine on the *trans*-di-iodo-compound, was dissolved in cold chloroform (25 ml.), and sulphur dioxide bubbled through the dark red solution. The colour faded during the first 15 minutes and after about an hour had become light orange, and was then apparently unaltered. The solution was filtered, the chloroform removed at the pump, and the pinkish-brown residue recrystallised twice from benzene and light petroleum, pink needles being obtained, m. p. (and mixed m. p. with a pure specimen of *trans*-di-iodo-compound) 229°. Attempts to reduce the tetrahalogeno-compound by boiling with acetone, the method used by Mann and Purdie (*loc. cit.*) for the auric complexes, were not successful.

Bisdiphenylmethylarsinedibromodi-iodoplatinum(IV). Bisdiphenylmethylarsinedibromoplatinum(II) (m. p. 201°) (0·84 g.), dissolved in chloroform (30 ml.), was treated with iodine (0·25 g.) dissolved in carbon tetrachloride–chloroform (30 ml.; 1 : 1) and the yellow orange solution immediately turned dark red. Removal of most of the solvent at room temperatures at the pump gave glistening black crystals which disproportionated when attempts were made to carry out recrystallisation. The *compound* melts at 185°, and from the analysis (Found: C, 27·6; H, 2·5; Pt, 17·5. $C_{26}H_{26}Br_2I_2As_2Pt$ requires C, 28·3; H, 2·4; Pt, 17·8%) appears to contain traces of the tetraiodide. In view of their instability these complexes were not further investigated.

Sir William Ramsay and Ralph Forster Laboratories,
University College, London.

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171. *Studies in Co-ordination Chemistry. Part II. Trisarsine Complexes of Bivalent Platinum and Palladium.*

By R. S. Nyholm.

The compounds $PtBr_2,3AsR_3$ and $PdBr_2,3AsR_3$ (where AsR_3 is diphenylmethylarsine) have been isolated and their properties investigated. Although their solubility in organic solvents suggested that they were non-ionic covalent complexes, it was found that they dissolved in these solvents with dissociation. Electrical-conductivity measurements in acetone solution on the palladium compound support the view that they are salts of the triammine type, *i.e.*, $[Pd(AsR_3)_3Br]^+Br^-$.

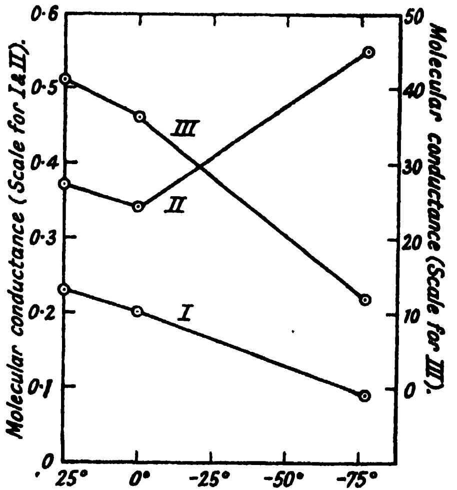
During an investigation of the tertiary arsine complexes of metal salts, two new complexes of bivalent platinum and palladium have been isolated of a type not previously described, and their properties were carefully investigated because their behaviour at first suggested that they might be examples of five-covalency similar to that observed by Jensen and Nygaard (*Acta Chem. Scand.*, 1949, 3, 474) in the nickel compound $NiBr_3,2PEt_3$. When preparing the compound $PtBr_2,2AsMePh_2$ by the action of diphenylmethylarsine on chloroplatinic acid in the presence of excess of sodium bromide, it was observed that excess of the arsine led to the formation of an orange crystalline *compound* of empirical formula $PtBr_2,3AsMePh_2$. Further investigation showed that this orange compound could be obtained readily by heating the bisarsine compound ($PtBr_2,2AsMePh_2$) with excess of arsine in alcohol solution under reflux, the trisarsine compound crystallising out on cooling. This complex dissolved readily in chloroform or benzene on shaking and was fairly soluble in acetone and warm alcohol. From the alcoholic solution the bisarsine compound was precipitated on cooling unless excess of arsine was present. The trisarsine compound melted at 151° as compared with 201° for the yellow bisarsine complex.

The corresponding *palladium* compound was prepared in a similar manner, starting with the orange *compound* $PdBr_2,2AsMePh_2$ and using a greater excess of arsine. Conditions were found to be more critical than in the case of the platinum compound, for the trisarsine complex dissociated very readily. It forms almost black crystals which melt at 109°, the colour changing to light orange; the bisarsine complex melts at 178°. The trisarsine compound dissolved very readily in organic solvents such as acetone, benzene, and chloroform, and was fairly soluble in alcohol, the black crystals giving an orange solution.

The molecular weights of both of these compounds were measured in a variety of solvents, benzene, bromoform, ethylene dibromide, and acetone being used; in the first three the determinations were cryoscopic, in the last ebullioscopic. In every case a molecular weight corresponding to half of the formula weight $MBr_2,3AsMePh_2$ (M = Pd or Pt) was observed because the compounds dissociated into one molecule each of arsine and the bisarsine compound; from benzene solution the bisarsine complexes were precipitated at the freezing point.

There are four obvious ways in which these compounds might be formulated: (*a*) as a molecular (lattice) compound of arsine and the bisarsine complex; (*b*) as a bridged complex of two octahedrally co-ordinated bivalent metal atoms, requiring a molecular formula $(MBr_2,3AsMePh_2)_2$; (*c*) as a salt of the type $[M(AsR_3)_3Br]^+Br^-$; (*d*) as a five-covalent complex in which the extra molecule of arsine forms a very weak bond to the metal atom by using the remaining 5*p* or 6*p* orbital. Since a solution of the compound shows some properties different from those expected of a mixture of its constituents, (*a*) is excluded; (*b*) is readily disposed of since neither molecular weight nor solubility lends any support, and in any case six-covalent complexes of bivalent palladium and platinum are very rare. Solubility in organic solvents and low melting point and the fact that such a complex should dissociate readily lent some support to (*d*), but the salt-like structure (*c*) has been finally accepted from studies on the conductivity of the palladium complex in acetone. The higher solubility of the palladium compound, particularly at low temperatures, made it preferable to the platinum complex for this purpose.

A solution of the palladium trisarsine complex in acetone has a very light orange colour at 25°, and is only very slightly darker than a solution of the bisarsine compound at the same concentration (M/100). When a solution of the bisarsine complex is cooled there is no perceptible change in colour but the trisarsine solution gradually deepens in colour as the temperature is reduced below −25°, and at about −78° the colour is deep red. As the trisarsine complex in the solid state is black with a red streak, it is reasonable to assume that recombination of the bisarsine complex and arsine to form the complex isolated in the solid state has taken place. This colour change is also observed if one cools similarly a mixture of free arsine and the bisarsine compound or a benzene solution of these two substances; the dark reddish-black mixture which is observed at low temperatures becomes orange again on warming to room temperatures. The great ease with which temperature caused dissociation, together with other properties mentioned above, led to the possibility of a weak covalent bond between the arsine and the metal. Conductivity measurements, however, show that at low temperatures an electrolyte is being formed. In the figure are shown the molecular conductivities of M/100-solutions of the bisarsine and the trisarsine complex in acetone at various temperatures, M/100-lithium bromide having been measured for comparison. Although for both lithium bromide and the bisarsine complex there is the expected decrease in conductivity as the temperature falls over the 100° range, yet the trisarsine complex shows a remarkable rise in conductivity below 0°. This increase in conductivity parallels the deepening in colour which occurs at the same temperature. No significance is attached to the actual conductance of $PdBr_2,2AsMePh_2$, and $PdBr_2,3AsMePh_2$ at 25°, it being due, no doubt, to traces of impurity or partial solvolysis; at −78°, however, it is clear that the amount of salt formation is more than sufficient to balance the natural decrease due to the fall in temperature. The amount of salt formation at −78° is still relatively small as judged by comparison with lithium bromide at the same temperature. One may conveniently represent the changes which take place when the trisarsine compound dissolves as follows:



I. M/100-$PdBr_2,2AsMePh_2$.
II. M/100-$PdBr_2,3AsMePh_2$.
III. M/100-LiBr.
(*All in acetone.*)

$$[Pd(AsR_3)_3Br]^+[Br]^- \xrightarrow{\text{Acetone}} PdBr_2,2AsR_3 + AsR_3 \underset{\text{Higher temperatures}}{\overset{\text{Low temperatures}}{\rightleftarrows}} [Pd(AsR_3)_3Br]^+ + Br^-$$

Reddish-black crystals. Light orange solution (room temperatures). Dark red solution (−78°).

One originally confusing observation was the fact that it was found possible to dissolve in benzene a higher molar concentration of the platinum trisarsine complex than of the bisarsine complex alone; this appeared especially unusual since all measurements showed that the trisarsine complex immediately dissociated into the bisarsine complex and arsine. However, the presence of arsine may enhance the solubility to some extent, but of greater importance is the probable formation of the *trans*-bisarsine complex initially on dissociation. This is much more soluble than the *cis*-form but the latter is gradually produced on standing. The yellow bisarsine compound used in the preparation is only slightly soluble in benzene at room temperatures and is hence undoubtedly the *cis*-isomer.

These compounds appear to be the first known examples of salts of the triammine type formed by tertiary arsines or phosphines with bivalent platinum or palladium. These ligands, unlike ammonia, have a great tendency to form non-ionic complexes but some salt-like compounds have been obtained; Jensen (*Z. anorg. Chem.*, 1936, **229**, 225) described salts of the type $[Pt(PR_3)_4]Cl_2$ and $[Pt(PR_3)_4][PtCl_4]$ which passed over into the monomeric covalent complexes $PtCl_2,2PR_3$ on heating in organic solvents but no evidence of a trisarsine or trisphosphine complex was obtained. Morgan and Yearsley (*J.*, 1925, **127**, 184) have described complexes of trialkylstibines similar to those isolated by Jensen. It is noteworthy that the iodide and bromide corresponding to the compounds described in this paper could not be obtained, and attempts to use trialkylarsines were unsuccessful; triphenylarsine also gave no trisarsine complex. Phenyldimethylarsine may be used instead of diphenylmethylarsine but the complexes are unsuitable for study because the arsine is very readily oxidised in air. The isolation of the compounds described in this paper must be ascribed to peculiarly favourable conditions of solubility not found with the other arsines or anions.

Like all bivalent complexes of palladium and platinum which have been measured, these trisarsine compounds are diamagnetic.

EXPERIMENTAL.

Bisdiphenylmethylarsinedibromopalladium(II).—Anhydrous palladous chloride (0·66 g.), dissolved in distilled water (33 ml.) containing a few drops of 10N-hydrochloric acid, was treated with sodium bromide (10 g.) in water (30 ml.) and diphenylmethylarsine (1·45 g.) in alcohol (150 ml.), and the solution heated on the water-bath. The initial yellow precipitate slowly redissolved on heating to form a reddish solution. After about ½ hour an orange precipitate gradually formed which was filtered off (2·1 g.) after several hours' heating on the water-bath, washed with cold aqueous alcohol and finally with water, and recrystallised from alcohol; m. p. 178° (Found: C, 41·2; H, 3·4; Pd, 14·0. $C_{26}H_{26}Br_2As_2Pd$ requires C, 41·3; H, 3·4; Pd, 14·1%). The *compound* crystallises as sparkling orange plates, readily soluble in chloroform or benzene, fairly soluble in acetone, but only slightly soluble in cold alcohol. Like all similar bisarsine compounds of palladium it is undoubtedly the *trans*-isomer.

Trisdiphenylmethylarsinemonobromopalladium(II) *Monobromide*.—The foregoing compound (0·34 g.) was treated with diphenylmethylarsine (3·0 g.) in alcohol (40 ml.) and heated to boiling. All dissolved to an orange solution, but on cooling, the original bisarsine complex crystallised out. (It is necessary to get concentrations just correct, otherwise the trisarsine complex is not obtained.) The solution was again heated to boiling and about 30 ml. of alcohol were removed by boiling, and on cooling slowly, dark brownish-red, almost black crystals were obtained. Formation of these crystals was hastened if the cold solution was carefully seeded with a crystal of the pure compound. The complex was filtered off after the solution had been kept for 24 hours and washed several times with cold alcohol, in which it is slightly soluble. After drying in a vacuum desiccator the *compound* was obtained as black crystals with a reddish streak [Found: C, 47·2; H, 3·95; Pd, 11·0%; *M* (cryoscopic), in bromoform (0·494%), 452; in ethylene dibromide (0·833%), 477. $C_{39}H_{39}Br_2As_3Pd$ requires C, 47·4; H, 4·0; Pd, 10·9%; *M*, 1003]. It dissolved readily in most organic solvents except light petroleum and was quite insoluble in water. On heating the compound melts at 109°, the colour changing instantly from black to orange.

Bisdiphenylmethylarsinedibromoplatinum(II).—This compound, m. p. 201°, prepared as in Part I (preceding paper), was recrystallised twice before use from acetone (Found: C, 37·5; H, 3·1; Pt, 23·1. Calc. for $C_{26}H_{26}Br_2As_2Pt$: C, 37·0; H, 3·1; Pt, 23·1%).

Trisdiphenylmethylarsinemonobromoplatinum(II) *Monobromide*.—The foregoing compound (4·0 g.) was heated under reflux with diphenylmethylarsine (5 g.) dissolved in alcohol (200 ml.) for about 15 minutes. Practically all the bisarsine complex had then dissolved, the solution becoming orange. The solution was filtered hot, and on cooling, orange crystals of the *trisarsine* compound were deposited. These were filtered off and washed many times with alcohol; yield, 407 g. [Found: C, 43·0; H, 3·5; Br, 14·8; Pt, 17·9%; *M*, in bromoform (cryoscopic), 0·875% soltn., 567, 1·45% soltn., 587; in ethylene dibromide (cryoscopic), 1·21% soln., 548; in acetone (ebullioscopic), 1·81% soln., 541; 3·70% soln., 560; in benzene * (cryoscopic), 1·60% soln., 485; 1·84% soln. 478. $C_{39}H_{39}Br_2As_3Pt$ requires C, 43·0; H, 3·6; Br, 14·7; Pt, 17·9%; *M*, 1087]. The compound melts sharply at 151° if heated fairly rapidly, the colour changing on fusion from orange to yellow. When cooled, the orange colour returns but the m. p. is then 2—3° lower, indicating that dissociation products are present. The compound is quite insoluble in water, practically insoluble in cold alcohol, but moderately soluble in acetone. An acetone solution slowly deposits yellow crystals of the bisarsine compound unless excess of arsine is added. On shaking, the compound dissolves fairly readily in benzene, chloroform, bromoform, and ethylene dibromide, but it is quite insoluble in light petroleum. Although an acetone solution reacts immediately with silver nitrate solution, this is not taken as significant, for the bisarsine complex also reacts immediately with silver nitrate.

Magnetic susceptibility. This was measured in powder form and the compound was found to be diamagnetic with a specific susceptibility $\chi_{293^\circ K.} = -0{\cdot}46 \times 10^{-6}$.

Electrical conductivity. These measurements were carried out in a pipette-type cell of volume about 15 ml. The cell constant (0·0508 cm.$^{-1}$) was determined at 25° with M/100-potassium chloride. It was not re-determined at lower temperatures because only comparative values of conductivity were required. The acetone used was A.R., which was distilled over potassium permanganate, dried [$Mg(ClO_4)_2$], and fractionated. The specific conductivity (κ) was $2{\cdot}1 \times 10^{-7}$, $1{\cdot}75 \times 10^{-7}$, and $7{\cdot}3 \times 10^{-8}$ mho/cm.[3] at 25°, 0°, and −78°, respectively. The $PdBr_2,2AsMePh_2$ and $PdBr_2,3AsMePh_2$ were recrystallised twice before use and dried in a vacuum desiccator. The M/100-solutions were made up at 25°. After measurement of the conductivity of a solution at 25°, the cell was placed in a bath of distilled water and ice, and the conductivity measured at 0°. The cell was then placed in a long Dewar flask containing alcohol and solid carbon dioxide, the flask being stoppered to prevent the entry of moisture. Throughout all measurements the temperature was checked with a toluene thermometer which remained constant to within 1° of −78°.

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* The results in benzene are unreliable because the bisarsine compound crystallised out after about two determinations of the freezing point; the solution is supersaturated and this probably explains the larger depression.

The author gratefully acknowledges the loan of platinum used in the work described in Parts I and II from Messrs. Johnson, Matthey and Co. Ltd. He also wishes to acknowledge the award by the University of London of an Imperial Chemical Industries Fellowship, during the tenure of which these researches were carried out.

Sir William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1.
[*Received, November 7th, 1949.*]

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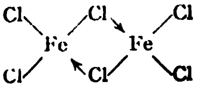
172. *Studies in Co-ordination Chemistry. Part III. Complexes of Iron with a Ditertiary Arsine.*

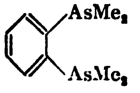
By R. S. Nyholm.

Complexes of ferric and ferrous halides with the chelating group *o*-phenylenebisdimethylarsine have been prepared and studied. Ferric chloride and bromide give rise to highly coloured salt-like compounds in which the univalent cation contains two halogen atoms and two molecules of the chelate group bound to the iron atom. The anion may be a halide ion or the ions $[FeCl_4]^-$ or $[FeBr_4]^-$. The tetrabromoferrate ion is converted readily into the bromide ion by treatment with water in acetone solution. Magnetic measurements have established that the cation has an effective magnetic moment which corresponds to one unpaired electron and it is concluded that the bonds to the iron are covalent, forming an octaheral complex; in the anions $[FeCl_4]^-$ and $[FeBr_4]^-$ a magnetic moment corresponding to five unpaired electrons is observed and in these ions the binding is thus ionic. The perchlorates have been prepared, and studies of their magnetic susceptibility support the above conclusions. When treated with iodides, the chloride complex is reduced to a diamagnetic ferrous compound which is formulated as a non-ionic octahedral complex with covalent bonds. The corresponding diamagnetic ferrous bromide and ferrous thiocyanate complexes have been prepared and studied. The implications of the magnetic measurements are discussed. Attempts to isolate halogen-bridged octahedral complexes were unsuccessful.

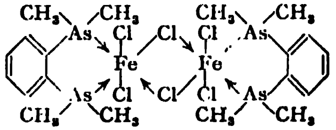
The complexes of iron halides with a ditertiary arsine have been studied as part of an investigation of Group VIII elements in various valency states with tertiary arsines. The chelating group *o*-phenylenebisdimethylarsine was chosen for this investigation for two reasons. Earlier investigations using diphenylmethylarsine had yielded complexes of ferric chloride which dissociated so readily in solution that it was possible only to speculate as to their structure (Nyholm, *J. Proc. Roy. Soc. N.S.W.*, 1944, **78**, 229) and a much more powerful ligand was needed. Jensen (*Z. anorg. Chem.*, 1936, **229**, 282) has reported that triethylphosphine, a stronger ligand than triethylarsine as a rule, does not co-ordinate with ferrous iron, and for this investigation the chelating group used was chosen because Chatt and Mann (*J.*, 1939, 1622) had shown that it forms very strong bonds, at least with bivalent palladium; it was also chosen in an attempt to isolate halogen-bridged complexes of ferric iron.



(I.)



(II.)



(III.)

Ferric chloride in the solid state has a layer structure with the ferric atom surrounded octahedrally by six chlorine atoms (Wooster, *Z. Krist.*, 1932, **83**, 35) but it sublimes readily at 285°, and below 440° its vapour pressure corresponds to the formula Fe_2Cl_6. In organic solvents like ether, alcohol, acetone, and pyridine, ferric chloride is monomeric but there is evidence for dimerisation in solvents like carbon disulphide, chloroform, and benzene (Wells, "Structural Inorganic Chemistry," Oxford, 1945, p. 139). These results have led to the general aceptance of a halogen bridge structure (I) for this dimer. The properties of ferric chloride make it inconvenient for a study of the properties of the bridge because of the ease with which it undergoes hydrolysis, but it was hoped that by using a chelate group the bridge could be stabilised with the formation of an octahedral complex as in (III). Tertiary arsines, and tertiary phosphines, are specially convenient for investigations of this nature, for their complexes are usually soluble in organic solvents and so permit of determination of molecular weights; furthermore, these ligands have not the troublesome consequences which often arise from the basic nature of ammonia and amines.

When the diarsine (II) reacts with anhydrous ferric chloride dissolved in alcohol or benzene a red colour immediately develops and a crimson precipitate is obtained. The presence of a little water does not affect the reaction, which is very sensitive, the red colour being formed with only traces of ferric chloride, and under the right conditions precipitation of the ferric iron is almost quantitative. The *compound* has the empirical formula $FeCl_3,C_6H_4(AsMe_2)_2$; it melts at 219°, and dissolves readily in nitromethane, acetone, and nitrobenzene. The molecular weight was determined ebullioscopically in acetone and cryoscopically in nitrobenzene and some association was observed, *x* in the formula $[FeCl_3,C_6H_4(AsMe_2)_2]_x$ being found to vary between 1·1 and 1·4 according to the solvent and the concentration. The compound is stable in air and does not react with moisture unless dissolved in acetone and treated with a fairly large amount of water, whereupon hydrolysis takes place. The corresponding *bromide* has been prepared and has a deep chocolate-brown colour; it melts at 209° and has properties similar to those of the chloride except that it is very much less stable to water, which converts it very readily into the green *salt* $[FeBr_2,2C_6H_4(AsMe_2)_2]^+$ Br^-. The facts that both the chloride and the bromide melted and dissolved in certain organic solvents at first seemed to exclude a salt-like structure, and a bridged structure (III) seemed likely since dissociation of halogen bridges in the solvents used for the molecular weights is not uncommon. However, it was not possible to split the bridge with such co-ordinating groups as pyridine, triethylarsine, or *p*-toluidine, and the magnetic measurements were difficult to interpret on such a hypothesis.

Magnetic-susceptibility measurements showed that both the chloride and the bromide were strongly paramagnetic, with an effective magnetic moment of about 4·6 Bohr magnetons both in the solid state and in acetone solution. This value would correspond to between three and four unpaired electrons if it is assumed that the whole of the moment may be attributed to spin alone. Pauling ("Nature of the Chemical Bond," N.Y., 1945, 2nd edition, p. 115) predicts that a moment of 1·73 B.M. should be found for octahedral covalent complexes of ferric iron using d^2sp^3 bonds, owing to the presence of one unpaired electron in the 3*d* shell; an example of this type of complex is potassium ferricyanide, for which the moment of 2·33 B.M. has been reported, the larger value being accounted for by orbital contribution. On the other hand, ionic complexes of ferric iron have a predicted magnetic moment of 5·92 B.M. due to the presence of five unpaired electrons; an example of this type of complex is the salt $(NH_4)_3FeF_6$ for which a moment of 5·9 B.M. has been reported. In Table I are shown the electronic arrangements and calculated magnetic moments for various types of ferrous and ferric complexes. The most unusual value of 4·6 B.M. for the complexes described above would be found in compounds in which both covalent and ionic binding were present, and with this idea in mind alternative methods for formulating these complexes were examined.

TABLE I.

Calculated magnetic moments for various types of iron complexes.

Complex.	Electronic arrangement. 3*d*.	4*s*.	4*p*.	Calculated * magnetic moment (μ).
Ferric covalent octahedral (d^2sp^3 bonds)	[↓↑][↓↑][↓][↓↑][↓↑]	[↓↑]	[↓↑][↓↑][↓↑]	1·73
Ferric ionic, octahedral or tetrahedral ...	[↓][↓][↓][↓][↓]	[ ]	[ ][ ][ ]	5·92
Ferric covalent planar (dsp^2 bonds)	[↓↑][↓][↓][↓][↓↑]	[↓↑]	[↓↑][↓↑][ ]	3·88
Ferrous covalent octahedral (d^2sp^3 bonds)	[↓↑][↓↑][↓↑][↓↑][↓↑]	[↓↑]	[↓↑][↓↑][↓↑]	0·00
Ferrous ionic, octahedral or tetrahedral	[↓↑][↓][↓][↓][↓]	[ ]	[ ][ ][ ]	4·90
Ferrous covalent planar (dsp^2 bonds)......	[↓↑][↓↑][↓][↓][↓↑]	[↓↑]	[↓↑][↓↑][ ]	2·83

* These values are calculated on the assumption that the whole of the moment is due to spin alone. Usually, there is a small orbital contribution which increases these values slightly; its effect is most marked with the lower values.

If it be assumed that the compounds are salts, the formulæ $[Fe\{C_6H_4(AsMe_2)_2\}_3][FeCl_6]$ and $[Fe\{C_6H_4(AsMe_2)_2\}_2Cl_2][FeCl_4]$ are possibilities. The former would contain the most unlikely square co-ordinated ferric iron, the cation having three and the anion five unpaired electrons (see Table I). The second formula, however, contains one octahedrally co-ordinated ferric atom, which would contain one unpaired electron if covalent bonds are present, and one ferric atom in which five unpaired electrons are expected; it will be shown that the susceptibility found is almost exactly that calculated for the second formula. This structure has also been confirmed by the preparation of the *perchlorate* of the cation. When an acetone solution of the *chloride* is treated with perchloric acid, a red precipitate is immediately formed, which has the formula $[Fe\{C_6H_4(AsMe_2)_2\}_2Cl_2][ClO_4]$. This compound has a magnetic moment of 2·34 B.M., which indicates one unpaired electron if due allowance is made for the orbital contribution, and shows that the cation is an octahedrally co-ordinated complex of ferric iron with covalent bonds. The magnetic susceptibilities of the various compounds are shown in Table II.

TABLE II.

Experimental magnetic susceptibilities of iron complexes.

Compound.	$\chi_M \times 10^{-6}$ (20°).	Diamagnetic correction.	$\chi_M \times 10^{-6}$ corr. for diamagnetism.	Magnetic moment (μ) per Fe atom.
1. $[Fe(Diarsine)_2Cl_2][FeCl_4]$	16,950	523	17,470	4·55
2. $[Fe(Diarsine)_2Cl_2][ClO_4]$	1,860	461	2,320	2·34
3. $[Fe(Diarsine)_2Cl_2]^+$	1,890	431	2,320	
4. $[FeCl_4]^-$ [from (1)–(3)]	15,060	94	15,150	5·98
5. $[Fe(Diarsine)_2Br_2][FeBr_4]$	17,100	598	17,700	4·57

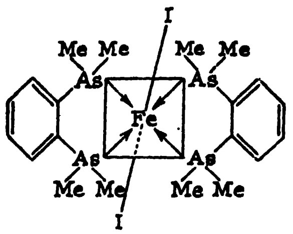
(The diamagnetic corrections used in this table were taken from Selwood, " Magnetochemistry," N.Y., 1943, p. 52.)

By subtracting the susceptibility of the chlorate ion from the susceptibility of the salt (2) (Table II), we obtain the susceptibility of the $[Fe(Diarsine)_2Cl_2]^+$ cation. If this value be then subtracted from the susceptibility of the compound (1) we obtain the susceptibility of the $[FeCl_4]^-$ ion and the magnetic moment calculated from this (μ = 5·98 B.M.) is in good agreement with that calculated for ferric iron with ionic bonds (μ = 5·92).

The behaviour of the ferric bromide *complex* (5) with water is readily explained from a consideration of its structure, for the first step one would expect is hydrolysis of the $[FeBr_4]^-$ ion; the product, $[Fe(Diarsine)_2Br_2]Br$, can be isolated because of its fairly low solubility in aqueous acetone. The corresponding chloride complex could not be isolated. The addition of a considerable amount of water to an acetone solution of the chloride (1) caused no change in colour or any immediate precipitate, although on long standing a brownish precipitate consisting chiefly of ferric hydroxide was obtained, which indicated complete breakdown of the compound. It is quite possible that the compound $[Fe(Diarsine)_2Cl_2]Cl$ is too soluble to be isolated under the conditions employed. The solubility of a salt like $[Fe(Diarsine)_2Cl_2][FeCl_4]$ in acetone, nitrobenzene, and nitromethane is explained by the high dielectric constants of these liquids; in spite of the large organic molecules which go to make up their structure, these compounds are quite insoluble in benzene and chloroform, and their solubility in such good ionising solvents as those mentioned above must be taken as a significant indication of their structure. The molecular weights which are found in nitrobenzene and acetone show that the molecules are largely ionised in these solvents.

The failure to obtain a stabilised halogen-bridge complex with this diarsine chelating group seems to indicate that such octahedral bridged complexes must be most unstable. The conditions used appeared most favourable for the formation of such a compound; if ferric chloride exists in benzene as a halogen-bridged molecule, then addition of the chelate might be expected to give the bridged octahedral complex readily, since addition of the diarsine would merely involve increasing the co-ordination number of the ferric atom from four to six without affecting the bridge.

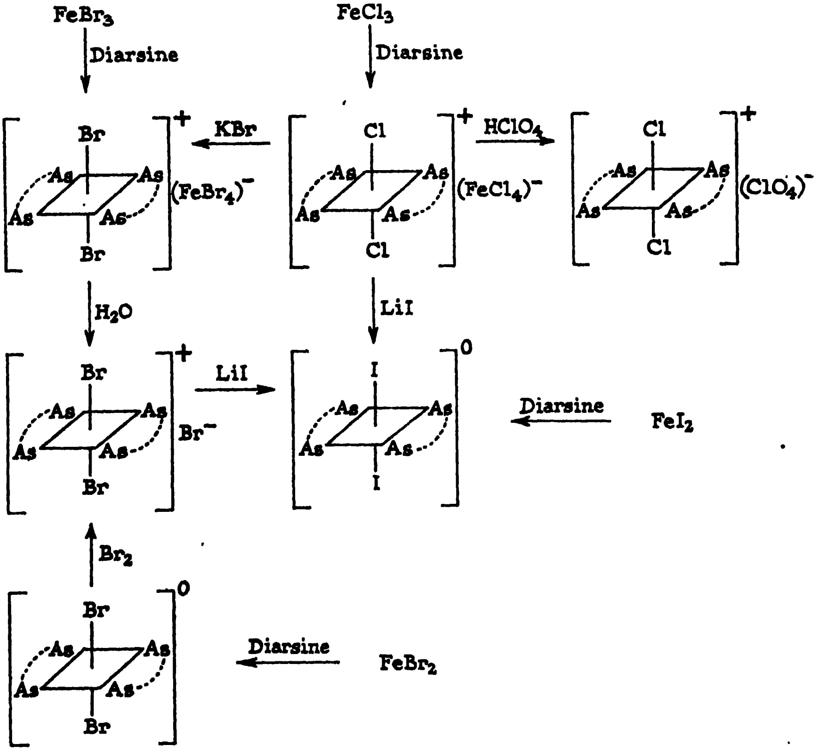
Attempts to isolate the ferric iodide salts resulted in the formation of a non-ionic complex of ferrous iron. The reaction between ferric iodide and the diarsine cannot be carried out directly owing to the instability of the former, so replacement of the chlorine from the compound $[Fe(Diarsine)_2Cl_2][FeCl_4]$ by the addition of lithium iodide in acetone solution was attempted. The dark solution quickly precipitated a yellow compound of empirical formula $Fe(Diarsine)_2I_2$ which was slightly soluble in acetone and chloroform, but solubilities were too low to enable one to carry out a molecular-weight determination. Since the compound is found to be diamagnetic, formulation as a planar four-covalent salt of the type $[Fe(Diarsine)_2]^{++} I^-_2$ is clearly excluded



(IV.)

because the use of dsp^2 bonds would require the presence of two unpaired electrons, making the compound paramagnetic (see Table I). The *compound* is thus a six-covalent non-ionic octahedral complex of ferrous iron with d^2sp^3 bonds (IV). This compound is one of the few examples known of diamagnetic, octahedral, non-ionic ferrous complexes; salt-like diamagnetic complexes of ferrous iron included the well-known red tris-*o*-phenanthroline and trisdipyridyl compounds. This compound appears to arise from the self-oxidation and -reduction of the unstable salt $[Fe(Diarsine)_2I_2]^+ I^-$, for the solution at first turns black on treatment with lithium iodide and then lightens and precipitates the ferrous complex. This black colour is also observed when a suspension of $[Fe(Diarsine)_2I_2]$ in alcohol is treated with iodine; a black precipitate is formed but the compound decomposed during attempts at its isolation. The ferrous complex may also be prepared by shaking together ferrous iodide and the diarsine in aqueous-alcoholic solution, the yellow ferrous iodide complex being quickly precipitated. The corresponding ferrous bromide complex may be prepared in a similar way and is also diamagnetic. When treated with bromine water, the ferrous bromide complex turns green immediately, with formation of the ferric salt $[Fe(Diarsine)_2Br_2]^+ Br^-$. The corresponding ferrous chloride complex was not isolated, but on shaking together a mixture of ferrous chloride and the diarsine in aqueous alcohol an immediate red colour was observed, and in the presence of air a copious precipitate of the ferric compound $[Fe(Diarsine)_2Cl_2][FeCl_4]$ was formed in a short time. In attempts to prepare a ferric thiocyanate complex the ferrous *compound* $[Fe(Diarsine)_2(CNS)_2]^0$ was isolated and, like the bromide and iodide, this compound is also diamagnetic and clearly an octahedral covalent complex. As with the iodide, reduction took place, and this is not difficult to understand in view of the oxidation potentials of the halogens; the oxidation potential for the reaction $2CNS^- \longrightarrow (CNS)_2$ (+0·77 v.) is much less than that for the reaction $2Br^- \longrightarrow Br_2$ (+1·07 v.) and not much more than that for the reaction $2I^- \longrightarrow I_2$ (+0·53 v.). Thus

TABLE III.



the order of stability to oxidation of the ferrous complexes is iodide > thiocyanate > bromide > chloride, which is the order of increasing oxidation potentials of the halogens.

In Table III are shown the relationships between the various complexes of ferrous and ferric iron. In all cases the two halogen atoms are shown as *trans*- for convenience; this is probably the case but no attempt has been made to prove it.

EXPERIMENTAL.

o-Phenylenebisdimethylarsine.—This was prepared by the method of Chatt and Mann (*J.*, 1939, 610). From *o*-nitroaniline (414 g.) after the six steps a yield of 22·6 g. of the diarsine, b. p. 157°/14 mm., was obtained (Found: C, 42·2; H, 5·4. Calc. for $C_{10}H_{16}As_2$: C, 42·0; H, 5·6%) as a colourless oil of unpleasant odour; it was kept sealed. Unlike the trialkylarsines, it is not readily oxidised in air and is more stable to air than phenyldimethylarsine.

Dichlorodi-(o-phenylenebisdimethylarsine)iron(III) *Tetrachloroferrate.*—Anhydrous ferric chloride (1·7 g.) was dissolved in purified spirit (75 ml.), and the solution filtered from traces of impurity and added with stirring to *o*-phenylenebisdimethylarsine (2·9 g.) dissolved in purified spirit (80 ml.). A crimson precipitate was immediately formed which was allowed to settle for about five minutes then filtered off and well washed with purified spirit, in which it was only very slightly soluble. An almost quantitative yield (4·5 g.) was obtained [Found: C, 26·6; H, 3·7; Cl, 23·5; Fe, 12·6%; *M* (cryoscopic) in 2·55% solution in nitrobenzene, 490; (ebullioscopic) in 2·76% solution in acetone, 536; in 3·87% solution in acetone, 637. $C_{20}H_{32}Cl_6As_4Fe_2$ requires C, 26·76; H, 3·6; Cl, 23·7; Fe, 12·46%; *M*, 897], m. p. 219° (decomp.). The *compound* was recrystallised from acetone–light petroleum. It dissolved readily in acetone, nitrobenzene, and nitromethane, was slightly soluble in alcohol and ethyl acetate, but completely insoluble in benzene, chloroform, ether, dioxan, and water. The compound was quite unaffected by water at room temperature. It could be prepared conveniently, also, by mixing solutions of the diarsine and ferric chloride dissolved in benzene, the crimson precipitate appearing immediately. The complex was stable indefinitely in air and no smell of arsine developed after many months' exposure to the atmosphere. Treatment of an acetone solution with silver nitrate solution caused decomposition of the compound, silver chloride being at once precipitated, and the colour changing from red to a deep blue which faded in about ½ hour. The substance responsible for this blue colour was not identified because of the rapid decomposition. When the acetone solution of the complex was treated with 1 mol. of pyridine, *p*-toluidine, or triethylarsine per iron atom there was no change in colour and the complex could be recovered unchanged by concentrating the solution. An acetone solution was not reduced by sulphur dioxde, but addition of perchloric acid to it gave an immediate precipitate of the perchlorate (see below).

Magnetic susceptibility. Magnetic susceptibilities were measured by the Gouy method on the magnet described by Baddar, Hilal, and Sugden (*J.*, 1949, 132). (*a*) The data for the powdered compound at 20° are in Table II; at 18·6°, $\chi = 18{\cdot}8 \times 10^{-6}$, whence, after correction as before, $\mu = 4{\cdot}52$; at 28·5°, $\chi = 18{\cdot}4 \times 10^{-6}$, whence, after correction, $\mu = 4{\cdot}55$.

(*b*) In acetone solution (M/25): at 23·8°, $\chi = 19{\cdot}7 \times 10^{-6}$, $\chi_M = 17{,}600 \times 10^{-6}$, and after correction, mean $\mu = 4{\cdot}61$; at 25·2°, $\chi = 20{\cdot}0 \times 10^{-6}$, $\chi_M = 18{,}000 \times 10^{-6}$, and after correction, mean $\mu = 4{\cdot}71$.

Dibromodi-(o-phenylenebisdimethylarsine)iron(III) *Tetrabromoferrate.*—*o*-Phenylenebisdimethylarsine (1·6 g.), dissolved in alcohol (100 ml.), was slowly added with rapid stirring to a freshly filtered solution of anhydrous ferric bromide (5 g.) dissolved in alcohol (30 ml.). (The ferric bromide was present in considerable excess and the order of addition given was followed to minimise formation of the green compound $[FeBr_2,2C_6H_4(AsMe_2)_2]Br$ described below.) A brown precipitate was formed immediately, and this was filtered off and washed many times with alcohol to remove excess of ferric bromide and any of the green compound, which is soluble in alcohol. The filtrate was finally very pale green owing to the presence of a small amount of the green compound formed by hydrolysis. The *tetrabromoferrate* (3·3 g., nearly quantitative) [Found: C, 20·8; H, 3·0; Br, 41·3; Fe, 9·7%; *M* (cryoscopic) in 2·73% solution in nitrobenzene, 692; (ebullioscopic) in 4·24% solution in acetone, 820; in 6·42% solution in acetone, 850. $C_{20}H_{32}Br_6As_4Fe_2$ requires C, 20·6; H, 2·58; Br, 41·25; Fe, 9·6%; *M*, 1164] was purified by recrystallisation from acetone–light petroleum. It dissolved readily in acetone, nitrobenzene, and nitromethane, forming a solution which was brown if dilute and red when concentrated. The compound formed brown shimmering crystals, m. p. 207° (decomp.), which under the microscope were seen to consist mainly of flat rhombs. The compound was completely insoluble in benzene, chloroform, ether, dioxan and organic solvents other than those mentioned above. Although it is insoluble in water it slowly hydrolysed to form the green salt $[FeBr_2(Diarsine)_2]Br$ and this green compound was also formed when water was added to a solution of the compound in acetone. An acetone solution of the complex reacted immediately with silver nitrate solution to precipitate silver bromide, the solution first turning green, then blue; the colour faded entirely in about 15 minutes.

Magnetic susceptibility. At 20°, see Table II. At 27·3°, $\chi = 14{\cdot}3 \times 10^{-6}$, whence, after correction, mean $\mu = 4{\cdot}57$.

Dibromodi-(o-phenylenebisdimethylarsine)iron(III) *Monobromide.*—Anhydrous ferric bromide (2 g.) was dissolved in alcohol (30 ml.), and the solution filtered and added with vigorous stirring to a solution of *o*-phenylenebisdimethylarsine (1·0 g.) dissolved in alcohol (75 ml.). A green compound was precipitated in a dark solution and a small amount of the brown ferribromide complex was formed also. The green precipitate had a characteristic appearance as shimmering, finely divided crystals. The mixture was then treated with distilled water with vigorous stirring until the brown colour disappeared, leaving only a green precipitate in a green solution. The solution was filtered quickly and the compound washed several times, first with small quantities of aqueous alcohol and finally with water. The minimum quantity of alcohol had to be used because of the high solubility of the compound in this solvent. After a final washing with light petroleum, the *compound* was obtained as microcrystalline rods. Recrystallisation was difficult, for attempts at purification from acetone–light petroleum gave the brown ferribromide; also, contact with water for very long caused hydrolysis. The compound was nevertheless obtained fairly pure by starting with freshly filtered solutions and filtering rapidly after treatment with water. It probably still contained traces of ferric hydroxide formed by hydrolysis, as shown by the iron value (Found: C, 27·6; H, 3·7; Br, 27·3; Fe, 6·7. $C_{20}H_{32}Br_3As_4Fe$ requires C, 27·7; H, 3·7; Br, 27·7; Fe, 6·5%). The compound dissolved readily in alcohol, acetone, and warm water to a green solution. Boiling with insufficient alcohol to dissolve it caused some formation of the brown complex. It was practically insoluble in all other organic solvents. Treatment of an alcoholic solution with silver nitrate solution gave an immediate precipitate of silver bromide followed by development of a blue colour which faded rapidly.

Dichlorodi-(o*-phenylenebisdimethylarsine*)*iron*(III) *Perchlorate*.—The tetrachloroferrate (2·8 g.), prepared as above, was dissolved in acetone, and the solution filtered and treated at once with excess of perchloric acid (30%). The solution was well stirred and almost immediately a red crystalline precipitate of the *perchlorate* was obtained. This was filtered off after a few minutes and well washed with alcohol, in which it is practically insoluble. It was then dried in a vacuum desiccator, yield 2·0 g. [Found: C, 30·3; H, 4·3; Cl, 8·8; Fe, 7·0. $C_{20}H_{32}O_4Cl_3As_4Fe$ requires C, 30·1; H, 4·0; Cl, 8·9 (excluding Cl present in the ClO_4 ion), Fe, 7·0%]. It was slightly soluble in acetone and fairly soluble in nitrobenzene, but quite insoluble in water or organic solvents like chloroform or benzene. When heated the compound did not melt but decomposed violently about 210°.

Magnetic susceptibility. See Table II.

Di-iododi-(o*-phenylenebisdimethylarsine*)*iron*(II).—The tetrachloroferrate complex (1·35 g.), dissolved in acetone (70 ml.) and filtered from traces of impurity, was treated with lithium iodide (2 g.; excess) dissolved in acetone (30 ml.). The red solution immediately became dark brownish-red and finally brown. After 3 minutes' vigorous stirring, golden-yellow crystals were precipitated. These were filtered off, well washed with acetone, a little water, then finally with alcohol, and dried in a vacuum desiccator; yield 0·7 g. (Found: C, 27·2; H, 3·7; I, 29·3; Fe, 6·7. $C_{20}H_{32}I_2As_4Fe$ requires C, 27·2; H, 3·6; I, 28·8; Fe, 6·4%), a little more of the *complex* remaining dissolved in the acetone. In all other solvents the complex was quite insoluble. An acetone solution gave a precipitate with silver nitrate solution on warming. When heated the compound did not melt but began to darken at 250° and decomposed above 300°. This compound could also be prepared by shaking together for a few minutes an alcoholic solution of the arsine with an aqueous solution of ferrous iodide.

Magnetic susceptibility. $\chi = -0{\cdot}3 \times 10^{-6}$ whence $\mu = 0$.

Dibromodi-(o*-phenylenebisdimethylarsine*)*iron*(II).—Ferrous sulphate heptahydrate (0·6 g.) and sodium bromide (0·8 g.) were dissolved in air-free distilled water (20 ml.) containing one drop of 10N-hydrochloric acid and added to a solution of *o*-phenylenebisdimethylarsine (1·0 g.) dissolved in alcohol (20 ml.). Most of the arsine was immediately precipitated as an oil, and the solution developed a pale green colour owing to the presence of a little ferric salt. The mixture was well shaken in a 100-ml. stoppered flask for about ½ hour with frequent warming on the water-bath; most of the arsine had then dissolved and a yellow precipitate had started to form. After 24 hours with occasional shaking and heating, the residue was filtered off and well washed, first with alcohol and finally with distilled water until the washings gave no precipitate with silver nitrate. After a final washing with alcohol it was dried in the vacuum desiccator. The bright yellow *complex* (Found: C, 31·5; H, 4·6; Br, 20·5; Fe, 7·0. $C_{20}H_{32}Br_2As_4Fe$ requires C, 30·4; H, 4·1; Br, 20·2; Fe, 7·1%) was slightly soluble in alcohol and chloroform but could not be recrystallised. It was quite insoluble in all other common solvents. The alcoholic solution reacted with silver nitrate on warming. Bromine immediately oxidised the complex to the green ferric salt $[FeBr_2,2C_6H_4(AsMe_2)_2]Br$. On heating, the compound did not melt but decomposed near 300. It was diamagnetic but the susceptibility was not measured precisely because the yield (0·9 g.) was insufficient to fill the tube; the susceptibility was estimated at about $-0{\cdot}2 \times 10^{-6}$.

Dithiocyanatodi-(o*-phenylenebisdimethylarsine*)*iron*(II).—Anhydrous ferric chloride (1·6 g.) was dissolved in absolute alcohol (100 ml.), and the solution filtered and treated with a solution of ammonium thiocyanate (2·8 g.) in absolute alcohol (100 ml.). To the dark red solution was added *o*-phenylenebisdimethylarsine (2·9 g.) dissolved in absolute alcohol (50 ml.). The solution was well stirred and left for 5 minutes, a heavy purple powder being precipitated. This was filtered off and washed many times with absolute alcohol until the washings showed only a very pale green colour. After a final washing with water the *compound* was dried in the vacuum desiccator; yield, 3·1 g.; m. p. 293° (decomp.) (Found: C, 35·6; H, 4·4; N, 3·7; S, 8·6; Fe, 7·6. $C_{22}H_{32}N_2S_2As_4Fe$ requires C, 35·4; H, 4·3; N, 3·76; S, 8·6; Fe, 7·5%). This powder had a magnetic susceptibility of $+0{\cdot}17 \times 10^{-6}$ but after recrystallisation from chloroform and light petroleum this value fell to $0{\cdot}0 \times 10^{-6}$; the higher initial value was probably due to traces of ferric salt. The compound was slightly soluble in acetone and chloroform to a purple solution but was insoluble in water, benzene, light petroleum, and other common solvents. An acetone suspension reacted very slowly with silver nitrate to precipitate silver thiocyanate. When heated, the compound became lighter in colour above 200°. When finely divided the complex had a purplish-pink colour.

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Sir William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1.

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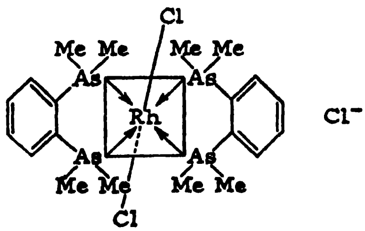
173. *Studies in Co-ordination Chemistry. Part IV. Complexes of Rhodic Halides with a Ditertiary Arsine.*

By R. S. Nyholm.

The complexes of tervalent rhodium halides with a chelating ditertiary arsine, *o*-phenylenebisdimethylarsine, have been prepared and studied. A series of salts have been isolated in which the univalent cation contains two molecules of the chelate group co-ordinated to the rhodium atom, two halogen atoms completing the octahedral configuration. All attempts to obtain complexes in which a halogen bridge connected two rhodium atoms were unsuccessful and it is concluded that such bridges, if formed, are unstable. The properties of the complexes are discussed.

In view of the ease with which bivalent rhodium formed binuclear halogen bridged complexes with tertiary arsines (Dwyer and Nyholm, *J. Proc. Roy. Soc. N.S.W.*, 1941, **75**, 127), the preparation of similar complexes of tervalent rhodium has been attempted. With tertiary arsines, bivalent rhodium halides gave rise to binuclear halogen bridged complexes of the type $[Rh(Hal)_2,3AsR_3]_2$ very readily and it was hoped that favourable circumstances for bridge formation with tervalent rhodium would be provided by the use of a suitable ditertiary arsine chelating group. Earlier work with diphenylmethylarsine (Dwyer and Nyholm, *ibid.*, p. 140) had shown that non-electrolytes of the formula $Rh(Hal)_3,3AsR_3$ could be isolated, but the use of a ditertiary arsine chelating group forces the rhodium either to bridge or to form a salt to complete a co-ordination number of six. It has been found, however, that the only complexes which could be isolated were salts containing two molecules of the chelate group to each rhodium atom and in which only part of the halogen was ionised. Variations in the method of preparation, such as changing the ratio of the reactants or refluxing the rhodium bisdiarsine salt with excess rhodic halide, failed to give the dimer. If formed, this dimer should be easily isolated, for binuclear complexes are usually much less soluble than the monomers from which they are derived. Most Group VIII metals, particularly those of the palladium and the platinum triad, have a tendency to form non-electrolytes with tertiary arsines rather than salts, and the formation of a salt in this case suggests that halogen bridges between tervalent rhodium atoms, if formed, are weaker than those between bivalent rhodium atoms.

The compounds isolated had the general formula $Rh(Hal)_3,2C_6H_4(AsMe_2)_2$; the chloride was investigated more than the *bromide* or the *iodide* because of its higher solubility in water, but the other two salts had similar properties. The compounds were formed in solution by heating the diarsine under reflux with the appropriate rhodic salt and were precipitated by addition of the corresponding acid. Since only part of the halogen was ionised, a salt-like structure for the complexes was presumed; then if a co-ordination number of six for the rhodium is assumed, the structure $[Rh(Hal)_2,2C_6H_4(AsMe_2)_2]Hal$ was expected. In the case of the chloride, this is as inset, the rhodium atom being octahedrally co-ordinated and the compound is *dichlorodi-(*o*-phenylenebisdimethylarsine)-rhodium*(III) *chloride*. This formulation has been confirmed by conductivity measurements and potentiometric titration with silver nitrate, a silver electrode being used. The molecular conductivity at a dilution of 1024 litres was 94 mhos; this figure is of the order expected for a strong electrolyte which forms two ions per molecule. The M/1024-solution was then titrated with silver nitrate in the presence of acetone and barium nitrate; the acetone was used to increase the sensitivity, and the barium nitrate the conductivity. The end-point of the titration occurred after only one of the three chlorine atoms had been precipitated (see figure), showing that only one chlorine atom was ionised. The small divergence from the calculated value is attributed to slight hydrolysis of the two covalently bound halogen atoms. In view of the dilution, the smallness of this hydrolysis is remarkable and indicates a very stable cation.



There is no evidence as to whether the two covalently bound chlorine atoms in the complex cation are *cis-* or *trans-*, but the latter is considered the more likely. This could be decided by attempts at optical resolution, for the *cis*-dichloro-compound should be capable of being resolved, but the *trans*-complex is inactive for it has a plane of symmetry. Complexes of tervalent cobalt and nickel in which similar cations are present will be described in Parts V and VI of this series.

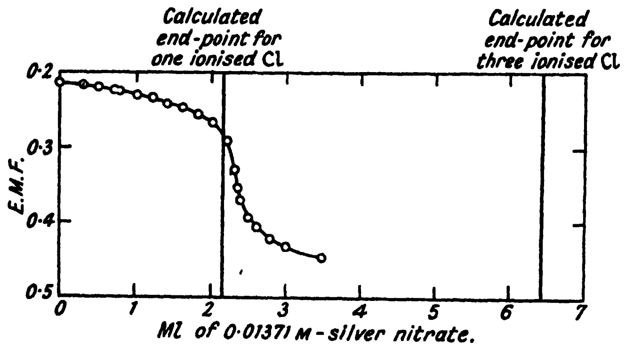
EXPERIMENTAL.

o-Phenylenebisdimethylarsine.—This was prepared as described in Part III (preceding paper).

Dichlorodi-(o-phenylenebisdimethylarsine)rhodium(III) *Monochloride.*—Sodium hexachlororhodate (0·65 g.), dissolved in distilled water (10 ml.), was treated with *o*-phenylenebisdimethylarsine (0·45 g.) in alcohol (70 ml.) containing hydrochloric acid (10N.; 5 ml.). (The ratio Rh : arsine was 1 : 1 in an attempt to obtain the bridged complex.) When the solution was heated, all the arsine dissolved, and after a few minutes the colour changed from red to light yellow, the complex salt being formed in solution. (An atmosphere of hydrogen, used initially, was later found unnecessary.) The solution was then heated under reflux for many hours in an attempt to effect bridging, but the only reaction was partial reduction to rhodium. The solution was filtered, and the filtrate concentrated to about 10 ml. and treated with concentrated hydrochloric acid. A yellow precipitate was obtained immediately and after cooling in ice this was filtered off and washed quickly with ice-cold dilute alcoholic hydrochloric acid and finally with small quantities of ice-cold water. It was then dried in the vacuum desiccator giving a yield of 0·4 g. The *compound*, recrystallised from aqueous alcohol containing a little hydrochloric acid, decomposed above 300° without melting (Found : C, 30·4; H, 4·2; Cl, 13·6; Rh, 13·1. $C_{20}H_{32}Cl_3As_4Rh$ requires C, 30·7; H, 4·1; Cl, 13·6; Rh, 13·1%). It was completely insoluble in benzene, chloroform, or light petroleum but dissolved readily in acetone or alcohol and was moderately soluble in warm water.

During the above preparation one occasionally obtained a heavy brown precipitate after a few seconds' refluxing which gradually re-dissolved on further heating. It was quite insoluble in all solvents and was probably the complex *salt* $[RhCl_2,2C_6H_4(AsMe_2)_2]_3[RhCl_6]$ (Found : Rh, 16·0. $C_{60}H_{96}Cl_{12}As_{12}Rh_4$ requires Rh, 16·2%). This compound appears to arise from the temporary coexistence of the two necessary ions, and it is significant that it is formed most readily in the presence of excess of sodium hexachlororhodate.

Potentiometric titration of M/1024-$[RhCl_2,2C_6H_4(AsMe_2)_2]Cl$, *with silver–silver chloride electrode.*



Dibromodi-(o-phenylenebisdimethylarsine)rhodium(III) *Bromide.*—Sodium hexachlororhodate (1·0 g.), dissolved in distilled water (13 ml.), was added to *o*-phenylenebisdimethylarsine (1·45 g.) in alcohol (60 ml.) containing concentrated hydrobromic acid (5 ml.); 30% hypophosphorous acid (2 ml.) was added to prevent the formation of bromine; it caused very little reduction of the rhodium salt. The solution was heated, and after a few minutes a brown sandy powder was precipitated which gradually dissolved on further refluxing to form an orange solution. After several hours' refluxing the solution was filtered from a very small amount of precipitate and concentrated to a small bulk on the water-bath. On cooling the residue (about 15 ml.) in ice, a yellowish-brown powder crystallised out. This was filtered off and washed with ice-cold alcohol and finally with ice-cold distilled water. It was dried in a vacuum desiccator. The *compound* (Found : C, 27·0; H, 3·8; Rh, 11·4. $C_{20}H_{32}Br_3As_4Rh$ requires C, 26·2; H, 3·5; Rh, 11·25%) did not melt but decomposed above 300°. It may be recrystallised from alcohol containing a little hydrobromic acid. An alcoholic solution precipitated only part of the bromine on treatment with silver nitrate.

Di-iododi-(o-phenylenebisdimethylarsine)rhodium(III) *Iodide.*—Sodium hexachlororhodate (2·0 g.), dissolved in water (25 ml.), was added to *o*-phenylenebisdimethylarsine (2·9 g.) in alcohol (125 ml.) containing hydriodic acid (57%; 10 ml.) just decolorised with hypophosphorous acid. To the mixture was added hypophosphorous acid (4 ml.), and on heating, the arsine quickly dissolved and a brownish-red powder was precipitated. This gradually dissolved on further refluxing and after 2 hours the solution was filtered and heated on the water-bath until the volume was about 50 ml. On cooling, beautiful crimson crystals were precipitated which were filtered off and washed many times with alcohol and finally with water. The *iodide* was much less soluble than the chloride or bromide and the addition of hydriodic acid when recrystallising from alcohol was not necessary. Two recrystallisations from alcohol gave an analytically pure specimen (Found : C, 23·0; H, 3·2; I, 36·2; Rh, 9·8. $C_{20}H_{32}I_3As_4Rh$ requires C, 22·7; H, 3·0; I, 36·2; Rh, 9·75%). The compound was completely insoluble in all organic solvents except alcohol and was insoluble in water. An alcoholic solution gave an immediate precipitate with silver nitrate, more silver iodide being formed on boiling owing, apparently, to rupture of the cation.

Conductivity of the Chloride Complex.—Measurements were carried out in a pipette-type cell of volume about 15 ml. and constant 0·0508 cm.$^{-1}$. The resistance of an M/1024-solution of the salt in this cell at 25° was 532 ohms. The conductivity of the water used was $3{\cdot}5 \times 10^{-6}$ mho/cm.[8]. From these data the molecular conductance at a dilution of 1024 litres is 94 mhos.

Potentiometric Titration.—30 Ml. of the M/1024-solution of the chloride complex were treated with Ana[illegible] acetone (100 ml.) and barium nitrate (1 g.), and the solution titrated with 0·01371M-silver nitrate fro[illegible] microburette, the solution being stirred vigorously throughout the titration. A silver–silver chloride electrode was immersed in the solution, and a reference electrode consisting of a silver–silver chloride electrode in saturated potassium chloride connected to the solution through an ammonium nitrate bridge. The result (see figure) shows clearly that only one of the three chlorine atoms is ionised.

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Sir William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1.
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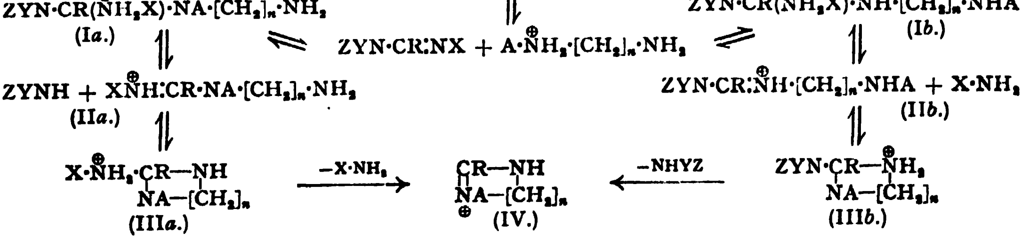
174. *Amidines. Part XIII. Preparation of 2-Substituted 4 : 5-Dihydroglyoxalines and Ring Homologues from Substituted Amidines and Alkylenediamines.*

By P. Oxley and W. F. Short.

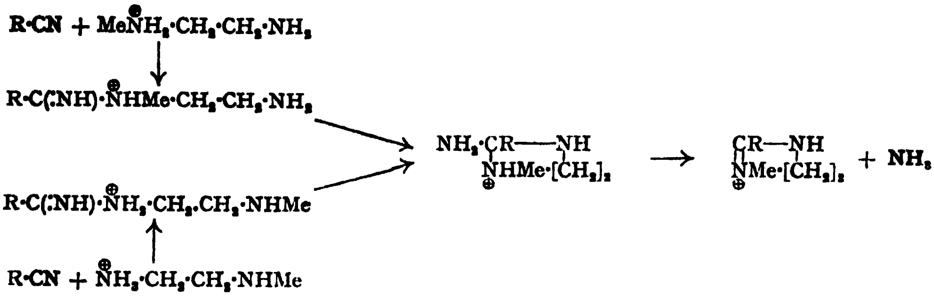
2-Substituted 4 : 5-dihydroglyoxalines and ring homologues are produced in good yield by heating substituted amidinium salts with an alkylenediamine. Ketoxime sulphonates and ethylenediamine also give 2-substituted 4 : 5-dihydroglyoxalines. Reaction mechanisms are proposed.

As a sequel to the investigation of the action of ammonia and monoamines on *N*-substituted amidinium salts and on ketoxime sulphonates (Parts IX and XI, *J.*, 1948, 1514; 1949, 449) we have examined the behaviour of these compounds with alkylenediamines. Miescher, Urech, Klarer, and Ciba (U.S.P., 2,252,721), Klarer and Urech (*Helv. Chim. Acta*, 1944, **27**, 1772), and Djerassi and Scholz (*J. Amer. Chem. Soc.*, 1947, **69**, 1688) have prepared a few 2-arylaminomethyl-, 2-hydroxymethyl-, and 2-aryloxymethyl-4 : 5-dihydroglyoxalines from ethylenediamine and the appropriate unsubstituted amidinium chloride in boiling alcohol, but the reaction of alkylenediamines with *N*-substituted amidines has not been investigated. We find that 2-substituted 4 : 5-dihydroglyoxalines and ring homologues are obtained in good yield by heating *N*-substituted amidinium salts with an alkylenediamine at temperatures within the range 50—180°. It is convenient to use the amidinium sulphonates, but chlorides, benzoates, and picrates have also been used. Aniline, nitrobenzene, and other solvents used in the ammonolysis of *N*-arylamidinium salts (Part XI, *loc. cit.*) could be employed in the reaction but were usually unnecessary. The amidine may have one, two, or three alkyl or aryl substituents on the nitrogen atoms, and the *N*-monoaryl derivatives are especially suitable owing to their ready availability (Part I, *J.*, 1946, 147; Part XI, *J.*, 1949, 449). The scope of the method is illustrated by the twenty-three examples in Table I, and it will be noted that *N*-alkylethylenediamines give 2-substituted 1-alkyl-4 : 5-dihydroglyoxalines. Since there is no reaction between an alkylenediamine and an *N*-substituted amidine at temperatures which yield a cyclic base when the amidinium salt is employed, it is probable that the reaction involves the production of orthoamidinium ions (I*a* and I*b*) from the amidinium salt, $ZYN{\cdot}CR{:}\overset{\oplus}{N}HX$, and the alkylenediamine, $A{\cdot}NH{\cdot}[CH_2]_n{\cdot}NH_2$, or from the reciprocal pair. The orthoamidinium


ZYN·CR:N⊕HX + A·NH·[CH₂]ₙ·NH₂
ZYN·CR(N⊕H₂X)·NA·[CH₂]ₙ·NH₂
(Ia.)
ZYN·CR(N⊕H₂X)·NH·[CH₂]ₙ·NHA
(Ib.)
ZYN·CR:NX + A·N⊕H₂·[CH₂]ₙ·NH₂
ZYNH + XN⊕H:CR·NA·[CH₂]ₙ·NH₂
(IIa.)
ZYN·CR:N⊕H·[CH₂]ₙ·NHA + X·NH₂
(IIb.)
X·N⊕H₂·CR—NH NA—[CH₂]ₙ
(IIIa.)
−X·NH₂
CR—NH NA—[CH₂]ₙ ⊕
(IV.)
−NHYZ
ZYN·CR—N⊕H₂ NA—[CH₂]ₙ
(IIIb.)

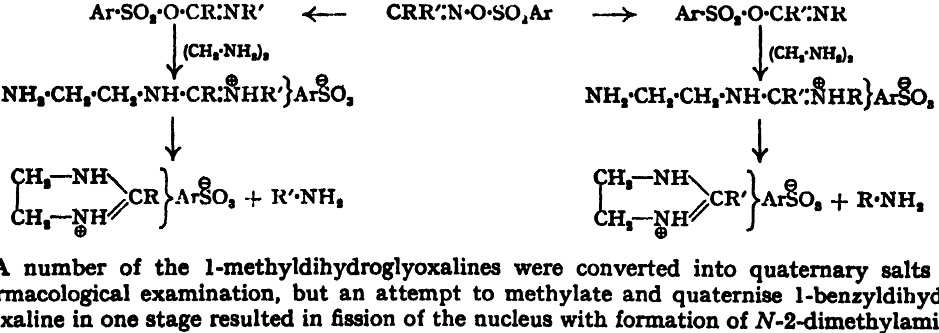
ions subsequently lose two molecules of amine (or one of ammonia and one of amine), as shown in the annexed scheme, representative of other routes in which the amines are eliminated in the reverse order and of structures with a different distribution of the positive charge. The intervention of cyclic compounds of the type (IIIa and b) is postulated since the dihydroglyoxaline resulting from the direct elimination of an amine from (IIb) would not necessarily contain the group A, whereas, in fact, 1-methyldihydroglyoxalines (IV; A = Me, $n = 2$), unaccompanied by the corresponding dihydroglyoxalines (IV; A = H, $n = 2$), are obtained from a substituted amidinium salt and *N*-methylethylenediamine.

The 2-arylmethyl-1-alkyl-4 : 5-dihydroglyoxalines enumerated in Table II were prepared by the interaction of the appropriate cyanide with a salt of *N*-methyl- or *N*-ethyl-ethylenediamine (Part VI, *J.*, 1947, 497), and the exclusive formation of dihydroglyoxalines containing a 1-alkyl group suggests the production of a cyclic intermediate which subsequently loses the elements of ammonia:



These *N*-alkyldihydroglyoxalines were examined by Gowdey (*Brit. J. Pharmacol.*, 1948, **3**, 254; 1949, **4**, 45) who found that, regardless of the action of the compounds not containing a *N*-substituent, they all cause a rapid rise of the blood-pressure and an increased heart-rate; moreover, the compounds unsubstituted on nitrogen affect the perivascular system directly whereas the *N*-alkyl derivatives affect the blood-pressure by a more central action, involving stimulation of the sympathetic ganglia, liberation of adrenaline, and direct action on the cardiac muscle.

Rearrangement of ketoxime sulphonates in presence of ethylenediamine gives 2-substituted dihydroglyoxalines, the ester of methyl ethyl ketoxime giving rise to both 2-methyl- and 2-ethyl-4 : 5-dihydroglyoxaline (compare Part IX, *J.*, 1948, 1514).



A number of the 1-methyldihydroglyoxalines were converted into quaternary salts for pharmacological examination, but an attempt to methylate and quaternise 1-benzyldihydroglyoxaline in one stage resulted in fission of the nucleus with formation of *N*-2-dimethylaminoethylphenylacetamide (*picrate*, m. p. 165·5—166°).

EXPERIMENTAL.*

Preparation of Alkylenediamine Salts.—The following salts were prepared by the method described in Part VI (*J.*, 1947, 502).

N-Methylethylenediammonium ditoluene-p-sulphonate, which separated from ethanol in colourless needles, m. p. 176° (Found: N, 6·6. $C_{17}H_{26}O_6N_2S_2$ requires N, 6·7%), was obtained from *N*-methylethylenediamine, prepared in 42% yield from ethylenediamine by modification of Aspinall's method (*J. Amer. Chem. Soc.*, 1939, **61**, 822). Direct methylation of ethylenediamine was not a practical method for the preparation of the *N*-monomethyl derivative (cf. Linsker and Evans, *J. Amer. Chem. Soc.*, 1945, **67**, 1581). Attempts to prepare a crystalline monotoluene-*p*-sulphonate of the *N*-methyl base were unsuccessful.

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* See also B.P. 614,032/1946.

N-*Ethylethylenediammonium ditoluene*-p-*sulphonate*, m. p. 158—159° (Found: N, 6·55. $C_{18}H_{28}O_6N_2S_2$ requires N, 6·5%) was prepared from *N*-ethylethylenediamine, obtained in 35% yield by Aspinall's method (*loc. cit.*).

Dihydroglyoxalines and Ring Homologues from N-*Substituted Amidinium Salts and Alkylenediamines.*—All the amidinium salts used in the experiments have been described in previous parts of the series. An equimolecular mixture of the *N*-substituted amidine, alkylenediamine, and acid (the last being introduced as free acid or as the amidinium, alkylenediammonium, or ammonium salt) was heated under the conditions recorded in Table I. Often no solvent was necessary, but reactions involving compounds of relatively high m. p. were facilitated by the addition of a small excess of alkylenediamine, or of a solvent such as aniline, dimethylaniline, or nitrobenzene. The salt of the heterocyclic base usually crystallised directly from the reaction mixture, but dilution with acetone or ether was occasionally necessary. One recrystallisation from methanol, *iso*propanol, or acetone was sufficient to give a product of constant m. p. The experiments recorded in Table I were conducted with 0·005—0·01 g.-mol. of the amidinium salt, and the yields are calculated on the amidine.

Preparation of 2-Substituted 1-Alkyl-4 : 5-dihydroglyoxalines.—Since dihydroglyoxalines and their 1-alkyl derivatives are of comparable basic strength, direct alkylation gives a mixture of dihydroglyoxaline, 1-alkyldihydroglyoxaline, and quaternary salt. The separation of this mixture is often laborious and yields are poor. Thus when 2-benzyl-4 : 5-dihydroglyoxaline (36 g.), methyl toluene-*p*-sulphonate (42 g., 1 mol.), and benzene (100 c.c.) were boiled for an hour, a heavy oil was obtained from which a mixture of 2-benzyl-4 : 5-dihydroglyoxaline and its 1-methyl derivative were liberated by 5N-sodium hydroxide. This mixture could not be satisfactorily separated into its constituents by distillation, but fractional crystallisation of the mixed picrates from methanol afforded hexagonal plates of 2-benzyl-1-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. 125—125·5° (15·5 g., 17%), identical with that obtained by the alternative method (see Table II).

The 1-alkyldihydroglyoxalines described in Table II were prepared from the appropriate cyanide, *N*-alkylethylenediamine (1 mol.), and ammonium toluene-*p*-sulphonate (1 mol.), according to the method described in Part VI (*loc. cit.*). No unsubstituted dihydroglyoxalines were formed in this reaction, and the 1-alkyldihydroglyoxalines were very easily purified and obtained in good yield.

1 : 8-*Di*-(1-*methyl*-4 : 5-*dihydro*-2-*glyoxalinyl*)*octane*. A mixture of octamethylene dicyanide (8·2 g.), *N*-methylethylenediammonium ditoluene-*p*-sulphonate (20·9 g., 0·5 mol.), and *N*-methylethylenediamine (3·7 g., 0·5 mol.) was heated at 190° for 2 hours. Crystallisation of the crude product from *iso*propanol afforded 1 : 8-di-(1-methyl-4 : 5-dihydro-2-glyoxalinyl)octane ditoluene-*p*-sulphonate (16·6 g., 53%). The properties of this salt and of the dipicrate are recorded in Table II.

1 : 2-*Di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*. Benzyl cyanide (11·7 g.), 3 : 6-diazaoctane-1 : 8-diamine ("triethylenetetramine") (7·3 g., 0·5 mol.), and ammonium toluene-*p*-sulphonate (18·9 g.; 1 mol.) were heated at 190° for 90 minutes. The resulting yellow gum was dissolved in water, made alkaline with 5N-sodium hydroxide, and extracted with chloroform. The light-brown residue (15 g.) obtained by evaporating the solvent was crystallised from benzene (15 c.c.) giving 1 : 2-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*, m. p. 131—132° (Found: N, 16·0. $C_{22}H_{26}N_4$ requires N, 16·2%) (7·5 g., 43%). The *dipicrate* had m. p. 235° (decomp.) (Found: N, 17·5. $C_{34}H_{32}O_{14}N_{10}$ requires N, 17·4%), and the *dihydrochloride*, obtained from the base and hydrogen chloride in *iso*propanol, separated as a crystalline powder, m. p. 275° (decomp.) (Found: N, 13·3. $C_{22}H_{28}N_4Cl_2$ requires N, 13·4%).

Dihydroglyoxalines from Ketoxime Sulphonates.—The ketoxime sulphonates were prepared as described in Part IX (*loc. cit.*).

2-*Phenyl*-4 : 5-*dihydroglyoxaline*. Ethylenediammonium dibenzenesulphonate, m. p. >360° (5·8 g., 32%), was deposited when benzophenone oxime benzenesulphonate (16·4 g.), anhydrous ethylenediamine (3 g., 1 mol.), and benzene (100 c.c.) were boiled for 1 hour and then cooled. The filtrate was washed with aqueous sodium hydroxide to remove benzenesulphonic acid, concentrated, and distilled on the steam-bath at 1 mm. to remove aniline (3 g., 64%). The residue consisted of *NN'*-diphenylbenzamidine, resulting from the action of aniline on the imidosulphonate produced by rearrangement of part of the oxime ester (Part IX, *loc. cit.*), and 2-phenyl-4 : 5-dihydroglyoxaline. Neutralisation of the mixture with aqueous benzenesulphonic acid afforded the sparingly soluble *NN'*-diphenylbenzamidinium benzenesulphonate, m. p. and mixed m. p. 218° (4 g., 19%), and 2-phenyl-4 : 5-dihydroglyoxaline, m. p. and mixed m. p. 101° (5·5 g., 77·5%), was isolated from the aqueous solution.

2-*Methyl*-4 : 5-*dihydroglyoxaline*. (i) Acetoxime benzenesulphonate (21·3 g.) ethylenediamine (6·0 g., 1 mol.), and toluene (50 c.c.) were boiled under reflux for ½ hour and the cold solution was extracted with water (25 c.c.). The aqueous layer was made alkaline with 5N-sodium hydroxide (50 c.c.), and the crude methyldihydroglyoxaline (7·9 g.) was collected in chloroform and converted into the picrate, m. p. 202° (24·0 g., 74·5%) with methanolic picric acid. Recrystallisation from water gave flat needles of 2-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 204° (Aspinall, *loc. cit.*; Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424).

(ii) 2-Methyl-4 : 5-dihydroglyoxalinium benzenesulphonate was the major product when methyl ethyl ketoxime benzenesulphonate (22·7 g.), ethylenediamine (6 g., 1 mol.), and benzene (50 c.c.) were boiled for 1 hour, but a little 2-ethyl-4 : 5-dihydroglyoxalinium benzenesulphonate was also formed. The bases, b. p. 100—103°/18 mm. (5·9 g.), were obtained by shaking the product with 5N-sodium hydroxide, extracting the aqueous solution with chloroform, and uniting the chloroform and benzene solutions. A solution of the mixed bases and picric acid (15·5 g.) in methanol (80 c.c.) deposited a crude picrate, m. p. 190°, after 1 hour at 0°, and recrystallisation from methanol afforded 2-methyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 204° (15·2 g., 48·5%). The original filtrate was evaporated to dryness and the residue was recrystallised from *iso*propanol, giving 2-ethyl-4 : 5-dihydroglyoxalinium picrate, m. p. and mixed m. p. 135—136° (2·5 g., 7·5%).

Preparation of Quaternary Salts of Dihydroglyoxalines.—2-*Benzyl*-1 : 3-*dimethyl*-4 : 5-*dihydroglyoxalinium salts*. An aqueous solution of the oily product which separated when 2-benzyl-1-methyl-4 : 5-dihydroglyoxaline (16·2 g.), methyl toluene-*p*-sulphonate (17·5 g., 1 mol), and dry benzene (100 c.c.) were boiled for 15 minutes, was treated with 2N-lithium picrate, and the solid (26 g.; m. p. 115—118°)

TABLE I.

Preparation of 2-substituted 4 : 5-dihydroglyoxalines and ring homologues from substituted amidines.

Heterocyclic compound.							Reaction :	
	Salt.•	M. p.	Yield, %.	Amidine.	Salt of amidine.•	Alkylene-diamine (mols.).	temp.	time (mins.).
4 : *5-Dihydroglyoxalines.*								
(1) 2-Methyl-	Picrate	204°	80	*N*-*cyclo*Hexyl-*N'*-ethylacet-	T	1·0	100°	30
(2) ,,	Picrate	204	88	*NN'*-Diphenylacet-	HCl	1·2	100	120
(3) 2-Ethyl-	Picrate	135—136	79	*NNN'*-Triethylpropion-	T	1·0	100	60
(4) 2-*n*-Butyl-	T	98	87	*N*-*p*-Tolylvaler-	T	1·33	100	30
(5) 2-Benzyl-	HCl	174	78	*N*-*cyclo*Hexylphenylacet-	HCl	1·7	*ca.* 180	5
(6) 2-*cyclo*Hexyl-	T *	171	97·5	*N*-Phenyl*cyclo*hexanecarboxy-	T	1·0	80	30
(7) 2-Phenyl-	T	165	73	*NNN'*-Trimethylbenz-	T	1·0	100	30
(8) ,,	Benzoate	115·5	77	*N*-Phenyl-*N'*-benzylbenz-	Benzoate	1·0	100	30
(9) ,,	B	141	92	*NN*-Pentamethylene-*N'*-phenylbenz-	B	1·7	100	60
(10) ,,	B	141	87	*N*-Phenylbenz-	B	1·7	100	120
(11) ,,	T	164	91	*N*-Phenylbenz-	T	1·0	100	120
(12) 2-*p*-Methoxyphenyl-	T	201	86	*N*-*p*-Tolyl-*p*-methoxybenz-	T	1·7	100	120
(13) ,,	T	201	81	*N*-*p*-Tolyl-*p*-methoxybenz-	T	1·7	140	60
(14) 2-*o*-Chlorophenyl-	T *	163	88	*N*-Phenyl-*o*-chlorobenz-	T	1·0	140	30
(15) 2-3' : 4'-Dimethoxyphenyl-	B *	192—192·5	88	*N*-Phenyl-3 : 4-dimethoxybenz-	B	1·5	100	60
(16) 2-2'-Naphthyl-	B *	188·5	82	*N*-*o*-Tolyl-2-naphth-	B	1·7	100	120
1-*Methyl-4 : 5-dihydroglyoxalines.*								
(17) 2-Benzyl-	HCl	88	74	*N*-*p*-Tolylphenylacet-	HCl	1·0	100	60
(18) 2-1'-Naphthyl-	Picrate	181·5	88	*N*-Phenyl-1-naphthylacet-	Picrate	1·35	130	5
3 : 4 : 5 : *6-Tetrahydropyrimidines.*								
(19) 2-Phenyl-	T	122	91	*N*-Phenyl-*N*-methylbenz-	T	1·0	55	60
(20) 2-(*p*-Methylsulphonylphenyl)-	T	187	96	*N*-Ethyl-*p*-methylsulphonylbenz-	T	1·0	100	60
2 : 7-*Diaza*cyclo*heptenes.*								
(21) 1-Benzyl-	Picrate	131	89	*N*-*p*-Tolylphenylacet-	T	1·0	100	60
(22) 1-(*p*-Methylsulphonylphenyl)-	Picrate	186	71	*N*-2-Pyridyl-*p*-methylsulphonylbenz-	Picrate	1·25	140	5
(23) 1-3'-Pyridyl-	Dipicrate *	177	86	*N*-Phenylnicotin-	B	1·25	100	30

* New compound. • B = Benzenesulphonate. T = Toluene-*p*-sulphonate.

Notes to Table I.

Except where otherwise indicated, the dihydroglyoxalines and ring homologues have been described in Part VI (*J.*, 1947, 497) and the known compounds were identified by comparison with authentic specimens.

(1), (2) Chitwood and Reid (*J. Amer. Chem. Soc.*, 1935, **57**, 2424) state that 2-methyl-4 : 5-dihydroglyoxalinium picrate has m. p. 205°. Aspinall (*ibid.*, 1939, **61**, 822) records m. p. 204°. See also Note (26) of Part IX (*J.*, 1948, 1521). (3) Chitwood and Reid (*loc. cit.*) and Aspinall (*loc. cit.*) state that the picrate has m. p. 137°. (5) The reaction mixture consisted of *N*-*cyclo*hexylphenylacetamidinium chloride (2·5 g.), ethylenediamine (1 c.c.), and nitrobenzene (5 c.c.). (6) *N*-Phenyl*cyclo*hexanecarboxyamidine (1·01 g.), 2-aminoethylammonium toluene-*p*-sulphonate (1·16 g.), and aniline (1 c.c.) gave *2-*cyclo*hexyl-4 : 5-dihydroglyoxalinium toluene-*p*-sulphonate*, m. p. 171° (Found: N, 8·7. $C_{16}H_{24}O_3N_2S$ requires N, 8·6%). (8) *2-Phenyl-4 : 5-dihydroglyoxalinium benzoate* consisted of rectangular plates, m. p. 115·5° (Found: N, 10·5. $C_{16}H_{16}O_2N_2$ requires N, 10·54%). (14) *2-*o*-Chlorophenyl-4 : 5-dihydroglyoxalinium toluene-*p*-sulphonate* crystallised in colourless plates, m. p. 163° (Found: N, 8·0. $C_{16}H_{17}O_3N_2ClS$ requires N, 7·9%). (15) 2-(3 : *4-Dimethoxyphenyl*)-*4 : 5-dihydro-*

Notes to Table I (contd.).

glyoxalinium benzenesulphonate had m. p 192—192·5° (Found : N, 7·9. $C_{17}H_{20}O_3N_2S$ requires N, 7·7%). (16) 2-2′-*Naphthyl*-4 : 5-*dihydroglyoxalinium benzenesulphonate* separated from *iso*propanol in slender needles, m. p. 188·5° (Found : N 7·9. $C_{19}H_{18}O_3N_2S$ requires N, 7·9%). (19) The reaction mixture consisted of *N*-phenyl-*N*-methylbenzamidine (1·05 g.), trimethylenediamine (0·37 g.), ammonium toluene-*p*-sulphonate (0·95 g.), and dimethylaniline (0·55 c.c.). (20) The reaction mixture consisted of *N*-ethyl-*p*-methylsulphonylbenzamidinium toluene-*p*-sulphonate (1·99 g.), trimethylenediamine (0·37 g.), and nitrobenzene (5 c.c.). (23) An aqueous solution of the reaction product from *N*-phenylnicotinamidine (0·4 g.), tetramethylenediamine (0·2 g.), and ammonium benzenesulphonate (0·35 g.) was made alkaline with 5N-sodium hydroxide, and the crude solid was purified by sublimation, giving 1-3′-*pyridyl*-2 : 7-*diaza*cyclo*heptene*, m. p. 102° (Found : N, 23·8. $C_{10}H_{13}N_3$ requires N, 24·0%). The *dipicrate* separated from methanol in long needles, m. p. 177° (Found : N, 20·0. $C_{22}H_{19}O_{14}N_9$ requires N, 19·9%).

TABLE II.

Preparation of 2-substituted 1-alkyl-4 : 5-dihydroglyoxalines from cyanides and N-*alkylethylenediamines.*

	Reaction,			Base.				Toluene-p-sulphonate.				Picrate.			
	temp.	time (hrs.).	Yield, %.	B. p. /mm.	Formula.	Found, N, %.	Reqd., N, %.	M. p.	Formula.	Found, N, %.	Reqd., N, %.	M. p.	Formula.	Found, N, %.	Reqd., N, %.
(1) 2-*Benzyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* [a]	190°	1½	92	107°/1	$C_{11}H_{14}N_2$	15·6	16·1	—	—	—	—	125—125·5°	$C_{17}H_{17}O_7N_5$	17·4	17·4
(2) 2-p-*Methoxybenzyl*-1-*methyl*-4 : 5-*dihydroglyoxaline*	190	1	69	—	—	—	—	114°	$C_{19}H_{14}O_4N_2S$	7·55	7·45	172·5	$C_{18}H_{19}O_7N_5$	16·4	16·2
(3) 2-1′-*Naphthylmethyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* [b]	190	1	87	—	—	—	—	—	—	—	—	181—181·5	$C_{21}H_{19}O_7N_5$	15·5	15·45
(4) 1 : 8-*Di*-(1-*methyl*-4 : 5-*dihydro*-2-*glyoxalinyl*)*octane*	190	2	53	—	—	—	—	149·5—150·5	$C_{30}H_{46}O_6N_4S_2$	9·1	9·0	167	$C_{28}H_{36}O_{14}N_{10}$	19·2	19·0
(5) 2-*Benzyl*-1-*ethyl*-4 : 5-*dihydroglyoxaline*	190	3	83	109—112/1·5	$C_{12}H_{16}N_2$	14·9	14·9	—	—	—	—	141	$C_{18}H_{19}O_7N_5$	17·1	16·8

[a] *Hydrochloride*, m. p. 88° (Found : N, 13·2. $C_{11}H_{15}N_2Cl$ requires N, 13·3%). [b] *Hydrochloride*, m. p. 241° (Found : N, 10·9. $C_{15}H_{17}N_2Cl$ requires N, 10·75%).

Notes to Table II.

The compounds described in the Table are new with the exception of 2-benzyl-1-methyl-4 : 5-dihydroglyoxaline which is mentioned, without physical constants, by Hartmann and Isler (*Arch. exp. Path.*, 1939, **192**, 141).

(1) The base gave erratic results on analysis by the Dumas method. (4) The preparation of this compound is described in detail below. (5) The base gave erratic results on analysis by the Dumas method. The hydrochloride was a gum but 2-*benzyl*-1-*ethyl*-4 : 5-*dihydroglyoxalinium sulphate* was obtained in deliquescent crystals, m. p. 151—152° (Found : N, 12·0. $C_{24}H_{34}O_4N_4S$ requires N, 11·8%).

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was crystallised from alcohol (50 c.c.) giving 25 g. of 2-*benzyl*-1 : 3-*dimethyl*-4 : 5-*dihydroglyoxalinium picrate*, m. p. 120°. This salt gave erratic results on Dumas analysis (Found : N, 17·4, 16·4, 17·4. $C_{18}H_{19}O_7N_5$ requires N, 16·8%). The picrate was treated with 5N-hydrochloric acid and, after removal of picric acid by extraction with benzene, the aqueous solution was evaporated to dryness and the residue crystallised from *iso*propanol giving large deliquescent octahedral crystals of the *chloride*, m. p. 210° (Found : N, 12·7. $C_{12}H_{17}N_2Cl$ requires N, 12·5%).

When 2-benzyl-4 : 5-dihydroglyoxaline (8 g.) was added to a stirred solution of methyl toluene-*p*-sulphonate (20 g., 2·15 mols.) in benzene (25 c.c.), the temperature rose to 33° in 15 minutes and then fell again, the solution remaining homogeneous. On addition of 5N-sodium hydroxide (20 c.c., 2 mols.) the temperature again rose to 30°. After being stirred for an hour, the product was neutralised (brilliant-yellow) with toluene-*p*-sulphonic acid, and the aqueous layer was separated and evaporated to dryness. The residue consisted of sodium toluene-*p*-sulphonate and an acetone-soluble gum (13 g.) which on treatment with 2N-lithium picrate afforded a solid *picrate*, m. p. 165·5—166°, probably the picrate of *N*-2-dimethylaminoethylphenylacetamide (Found : C, 50·0; H, 4·9; N, 16·0. $C_{18}H_{21}O_8N_5$ requires C, 49·7; H, 4·8; N, 16·1%).

The dimethotoluene-p-*sulphonate of* 1 : 2-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*ethane*. This separated as an oil when the dihydroglyoxaline (3·46 g.) and methyl toluene-*p*-sulphonate (3·72 g., 2 mols.) were boiled in benzene solution (20 c.c.). The quaternary *salt*, m. p. 167—169° (6·53 g., 91%), crystallised on trituration with acetone, and the m. p. remained unchanged after crystallisation from *iso*propanol (Found : N, 7·8. $C_{36}H_{42}O_6N_4S_2$ requires N, 7·8%). The corresponding *dimethopicrate*, prepared by double decomposition, separated from ethanol in flat needles, m. p. 175° (Found : N, 17·0. $C_{36}H_{36}O_{14}N_{10}$ requires N, 16·8%).

Methosalts of 1 : 8-*di*-(2-*benzyl*-4 : 5-*dihydro*-1-*glyoxalinyl*)*octane*. The oily base obtained from the dihydroglyoxalinium ditoluene-*p*-sulphonate (15·5 g.) and 2·5N-sodium hydroxide (50 c.c.) reacted exothermally with a solution of methyl toluene-*p*-sulphonate (10·2 g., 2·2 mols.) in benzene (10 c.c.), and the metho-salt separated as an oil which crystallised on manipulation. After recrystallisation from a mixture of methanol and acetone, the *dimethotoluene*-p-*sulphonate* (12 g., 74%) had m. p. 158—160° (Found : N, 8·7. $C_{32}H_{50}O_6N_4S_2$ requires N, 8·6%). The *dimethopicrate* separated from methanol in orange blades, m. p. 134° (Found : N, 18·2. $C_{30}H_{40}O_{14}N_{10}$ requires N, 18·3%).

2-p-*Hydroxy*- *and* 2-p-*Methoxy-benzyl*-4 : 5-*dihydroglyoxaline*, 2-*Benzylglyoxaline*, *and* 2-*Benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidine*.—*p*-Hydroxybenzyl cyanide (6·65 g.), prepared in 60% yield from *p*-aminobenzyl cyanide as described by Kossler and Hanke (*J. Biol. Chem.*, 1919, **39**, 585), and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g., 1 mol.) were heated at 155° for 1½ hours. The solid was crystallised from *iso*propanol (20 c.c.), giving unchanged 2-aminoethylammonium toluene-*p*-sulphonate (3 g.) and then 2-p-*hydroxybenzyl*-4 : 5-*dihydroglyoxalinium toluene*-p-*sulphonate* (11·0 g., 63%), m. p. 146—147°, unchanged after recrystallisation from water or alcohol (Found : N, 8·05. $C_{17}H_{20}O_4N_2S$ requires N, 8·0%). The *picrate* crystallised from water in rhombs, m. p. 161° (Found : N, 17·35. $C_{16}H_{15}O_8N_5$ requires N, 17·3%).

p-Methoxybenzyl cyanide (11·76 g.), b. p. 107—110°/1 mm., obtained in 91% yield by methylating the hydroxy-cyanide with methyl iodide and alcoholic sodium ethoxide, and 2-aminoethylammonium toluene-*p*-sulphonate (18·56 g., 1 mol.) afforded a solid when heated at 190° for 1 hour. After being triturated with acetone and recrystallised from *iso*propanol (60 c.c.) this solid afforded 2-p-*methoxybenzyl*-4 : 5-*dihydroglyoxalinium toluene*-p-*sulphonate* (20 g., 69%), m. p. 138° (Found : N, 7·8. $C_{18}H_{22}O_4N_2S$ requires N, 7·7%). The corresponding *picrate* had m. p. 119° (Found : N, 16·8. $C_{17}H_{17}O_8N_5$ requires N, 16·7%), and 2-p-*methoxybenzyl*-4 : 5-*dihydroglyoxaline* separated from benzene in flat needles, m. p. 121—122° (Found : N, 15·0. $C_{11}H_{14}ON_2$ requires N, 14·7%).

When 2-benzyl-4 : 5-dihydroglyoxaline (8 g.) was heated at 250° with a 40% cobalt–kieselguhr catalyst (1 g.) evolution of hydrogen was complete in 45 minutes. The product was separated from the catalyst by extraction with benzene, and was converted into the hydrochloride by shaking the benzene solution with 2N-hydrochloric acid (50 c.c.). The residue obtained by evaporating the aqueous solution was crystallised from *iso*propanol giving colourless, deliquescent needles of 2-*benzylglyoxalinium chloride* (7·0 g., 72%), m. p. 176° (Found : N, 14·2. $C_{10}H_{11}N_2Cl$ requires N, 14·4%). The picrate had m. p. 172° and the free base m. p. 125°; Sonn and Grief (*Ber.*, 1933, **66**, 1900) record 172° and 125—126°, respectively.

When benzyl cyanide (11·7 g.), trimethylenediammonium ditoluene-*p*-sulphonate (20·9 g.) and tetramethylenediamine (4·0 g.) were heated at 190° for an hour, and the base, liberated with 5N-sodium hydroxide (25 c.c.) and collected in benzene, was distilled, 2-*benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidine* (15·0 g., 86%) was obtained in colourless needles m. p. 114—114·5°, b. p. 135—136°/0·5 mm. (Found : N, 16·2. $C_{11}H_{14}N_2$ requires N, 16·1%). The *picrate* separated from methanol in prisms m. p. 174·5° (Found: N, 16·3, 16·9. $C_{17}H_{17}O_7N_5$ requires N, 17·4%). 2-*Benzyl*-3 : 4 : 5 : 6-*tetrahydropyrimidinium chloride*, prepared from the base and hydrogen chloride in acetone, had m. p. 210° (Found : N, 13·3. $C_{12}H_{15}N_2Cl$ requires N, 13·3%).

RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO., LTD.,
NOTTINGHAM.

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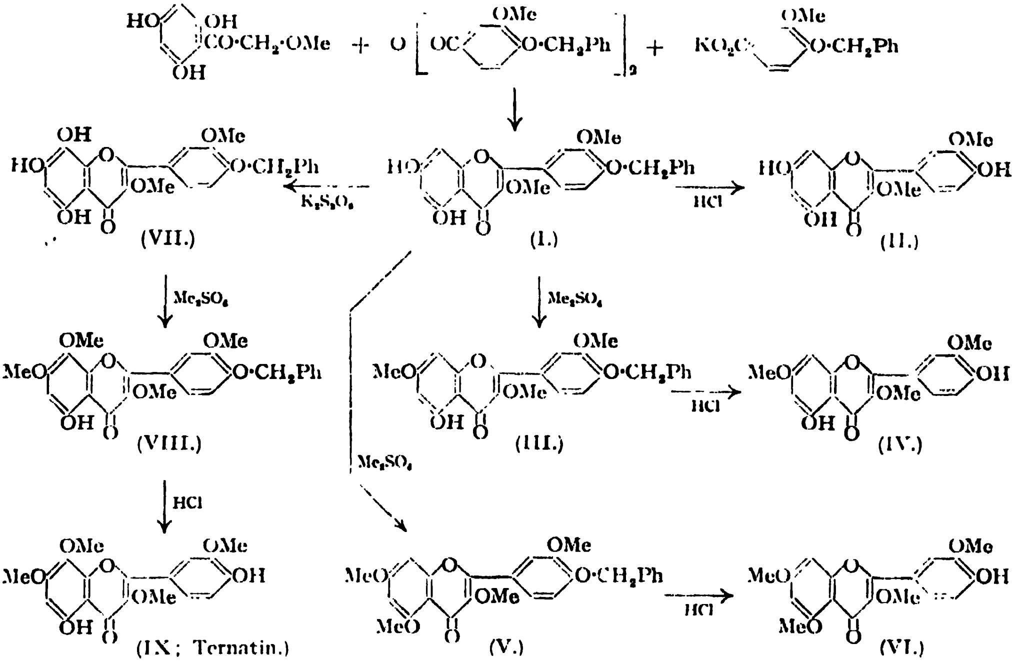
175. *Flavonols from the Bark of* Melicope ternata. *Part III. A Synthesis of Quercetin 3 : 3′-Dimethyl Ether, Quercetin 3 : 7 : 3′-Trimethyl Ether, Quercetin 3 : 5 : 7 : 3′-Tetramethyl Ether, Ternatin, and Related Benzyl Ethers.*

By LINDSAY H. BRIGGS and R. H. LOCKER.

The above compounds have been synthesised by combining Allan and Robinson's flavonol synthesis (*J.*, 1924, **125**, 2192) and Seshadri's recent methods of nuclear oxidation (*Proc. Indian Acad. Sci.*, 1948, **28**, *A*, 1).

BY combining the above flavonol synthesis, protection of appropriate free phenolic groups by formation of their benzyl ethers, and the nuclear oxidation with potassium persulphate (see Seshadri, *loc. cit.*, for summary), the 3 : 3′-*dimethyl*, 3 : 7 : 3′-trimethyl, and 3 : 5 : 7 : 3′-*tetramethyl ethers* of quercitin, and also ternatin (5 : 4′-dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone; cf. Part I, *J.*, 1949, 2157), have been synthesised according to the following scheme.

Condensation of *O*-benzylvanillic anhydride with ω-methoxyphloracetophenone in the presence of potassium *O*-benzylvanillate at 160—170° afforded 5 : 7-*dihydroxy*-4′-*benzyloxy*-3 : 3′-*dimethoxyflavone* (I), hydrolysed by hydrochloric acid–acetic acid to quercetin 3 : 3′-dimethyl ether (II). Partial methylation of (I) gave 5-*hydroxy*-4′-*benzyloxy*-3 : 7 : 3′-*trimethoxyflavone* (III), hydrolysed as before to quercetin 3 : 7 : 3′-trimethyl ether (IV), described by Kuhn and Low (*Ber.*, 1944, **77**, 202). Complete methylation of (I) produced *4′-benzyloxy-3 : 5 : 7 : 3′-tetramethoxyflavone* (V), hydrolysed as previously to quercetin 3 : 5 : 7 : 3′-tetramethyl ether. Nuclear oxidation of (I) with potassium persulphate (cf. Seshadri, *loc. cit.*, and Baker and Brown, *J.*, 1948, 2303 for the mechanism of the reaction) introduced a phenolic group at $C_{(8)}$, forming 5 : 7 : *8-trihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone* (VII) in poor yield, which was partly methylated to *5-hydroxy-4′-benzyloxy-3 : 7 : 8 : 3′-tetramethoxyflavone* (VIII). Hydrolysis of the last compound, as before, afforded 5 : 4′-dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone (IX), identical in all respects with ternatin, the structure of which, suggested in Part I (*loc. cit.*), is thus confirmed.



EXPERIMENTAL.

(All m. p.s are corrected.)

Methyl O-*Benzylvanillate*.—Methyl vanillate, m. p. 62°, was prepared from vanillin *via* vanillic acid (Pearl, *J. Org. Chem.*, 1947, **12**, 86), esterification being by methyl alcohol and sulphuric acid (Matsmoto, *Ber.*, 1878, **11**, 128). Methyl vanillate (85 g., 1 mol.) and potassium hydroxide (27·5 g., 1 mol.) were dissolved separately in hot methyl alcohol (total, 125 c.c.). Benzyl chloride (60 g., 1 mol.) was added, and the mixture heated under reflux for 5 hours and filtered hot. The potassium chloride was washed with hot methyl alcohol, the combined filtrate concentrated and cooled, whereupon long colourless prisms (95·5 g.) separated, m. p. 86—86·5° (after recrystallisation from alcohol) (Found: C, 70·5; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). Alkaline hydrolysis afforded *O*-benzylvanillic acid, m. p. 173·5—175·5° (Lovecy, Robinson, and Sugasawa, *J.*, 1930, 821), converted into the anhydride, m. p. 137·5—193·5°, by treatment with thionyl chloride and pyridine (*idem. ibid.*). The potassium salt of *O*-benzylvanillate was formed by mixing equimolecular quantities of the acid and potassium hydroxide in hot alcohol, and concentration. The silky needles which formed were very soluble in alcohol and decomposed and carbonised above 250°.

5 : *7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone*.—*O*-Benzylvanillic anhydride (38 g., 2·5 mols.), potassium *O*-benzylvanillate (13·8 g., 1·5 mols.), and *ω*-methoxyphloracetophenone (6·1 g., 1 mol.; Slater and Stephen, *J.*, 1920, **117**, 312) were powdered together and heated at 160—170° for 2 hours. The powdered cake was dissolved in alcohol (300 c.c.) and water (20 c.c.) containing potassium hydroxide (30 g.), and the solution was boiled for 10 minutes before the alcohol was distilled off under reduced pressure almost to dryness. A yellow precipitate (7·7 g.) formed when carbon dioxide was passed into the solution of the yellow residue in water (300 c.c.). Pale yellow needles separated, having m. p. 258—259° when crystallised from acetone (Found: C, 68·2; H, 4·9. $C_{24}H_{20}O_7$ requires C, 68·6; H, 4·7%). The *flavone* is insoluble in sodium carbonate or concentrated hydrochloric acid but soluble in 10% sodium hydroxide solution or concentrated sulphuric acid with a yellow and an intense yellow colour, respectively. It gives a brown colour with alcoholic ferric chloride solution and a strong red colour when reduced with magnesium, hydrochloric acid, and alcohol and also with sodium amalgam and alcohol followed by acidification.

5 : 7 : 4′-Trihydroxy-3 : 3′-dimethoxyflavone (*Quercetin* 3 : 3′-*Dimethyl Ether*).—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (100 mg.) was heated on the water-bath with glacial acetic acid (4 c.c.) and concentrated hydrochloric acid (2 c.c.) for an hour. The flocculent yellow precipitate, obtained by pouring the mixture into water, was coagulated by heating on the water-bath for ½ hour and crystallised 3 times from alcohol, yielding yellow plates, m. p. 257—258° (Found : C, 61·8; H, 4·2. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·2%). The *flavone* is slightly soluble in sodium hydrogen carbonate solution, readily soluble in sodium carbonate and hydroxide solution with a bright yellow colour. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. In a buffer at pH 9·8, a stable yellow colour is formed. A brown colour is given with alcoholic ferric chloride solution, and a strong red colour when reduced both with magnesium in concentrated hydrochloric acid and alcohol and with sodium amalgam and alcohol followed by acidification. The *triacetate* of the flavone was produced by dissolving 23 mg. in acetic anhydride (0·5 c.c.) and one drop of 60% perchloric acid and ½ hour's keeping. The product, formed by pouring into water, separated from ethyl or methyl alcohol in colourless needles, m. p. 199—200° (Found : C, 60·7; H, 4·5. $C_{23}H_{20}O_{11}$ requires C, 60·5; H, 4·4%).

5-Hydroxy-4′-benzyloxy-3 : 7 : 3′-trimethoxyflavone.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (320 mg.) was partly methylated by dissolving it in dry acetone (18 c.c.) and heating the mixture under reflux for 6½ hours with methyl sulphate (0·08 c.c., 1·1 mols.) and anhydrous potassium carbonate (2 g.). The acetone solution, together with washings of the insoluble salts, was concentrated, yielding yellow prisms (68 mg.), m. p. *ca.* 154°. The yellow insoluble salts were dissolved in water, acidified, and warmed to coagulate the product, a light yellow solid, m. p. 153—154° (175 mg.). The combined product was crystallised 3 times from alcohol, forming light-yellow plates of constant m. p. 151—152° (Found : C, 68·8; H, 5·3. $C_{25}H_{22}O_7$ requires C, 69·1; H, 5·1%). The *flavone*, typical of many flavones with a free 5-hydroxy-position, is insoluble in 10% sodium hydroxide solution. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. A brown colour is given with alcoholic ferric chloride solution, a scarlet colour with magnesium, hydrochloric acid, and alcohol, and a red colour with sodium amalgam and alcohol followed by acidification.

5 : 4′-Dihydroxy-3 : 7 : 3′-trimethoxyflavone (*Quercetin 3 : 7 : 3′-Trimethyl Ether*).—The preceding flavone (130 mg.) was hydrolysed for an hour at 100° with a mixture of glacial acetic acid (7 c.c.) and concentrated hydrochloric acid (3·5 c.c.). The product crystallised from alcohol in slender needles, m. p. 167—168·5°. Kuhn and Low (*loc. cit.*) record m. p. 169—170° for this compound. It is insoluble in sodium carbonate solution or concentrated hydrochloric acid, but soluble in 10% sodium hydroxide solution or concentrated sulphuric acid with a yellow coloration. A brown colour is given with alcoholic ferric chloride, and a scarlet colour both with magnesium, hydrochloric acid, and alcohol and with sodium amalgam and alcohol after acidification. The diacetate, prepared from 20 mg. as previously described, after successive crystallisation from ethyl and methyl alcohol, formed prismatic needles, m. p. 177·5—178° (Kuhn and Low, *loc. cit.*, record m. p. 174—175°).

4′-Benzyloxy-3 : 5 : 7 : 3′-tetramethoxyflavone.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (200 mg.) was completely methylated by heating in dry acetone solution (15 c.c.) with methyl sulphate (0·3 c.c., 6 mols.) and anhydrous potassium carbonate (1 g.) for 3 hours. The acetone solution and washings of the insoluble salts were concentrated and gave colourless crystals (170 mg.), which, after 2 crystallisations from alcohol, formed needles, m. p. 162—163° (Found : C, 69·5; H, 5·5. $C_{26}H_{24}O_7$ requires C, 69·6; H, 5·4%). The *flavone* is insoluble in 10% sodium hydroxide solution, slightly soluble in concentrated hydrochloric acid, and freely soluble in concentrated sulphuric acid with weak and intensely yellow colours, respectively. There is no colour with alcoholic ferric chloride solution, but a scarlet colour with magnesium, hydrochloric acid, and alcohol as well as with sodium amalgam and alcohol followed by acidification.

4′-Hydroxy-3 : 5 : 7 : 3′-tetramethoxyflavone (*Quercetin 3 : 5 : 7 : 3′-Tetramethyl Ether*).—The preceding flavone (110 mg.) was hydrolysed with glacial acetic acid (4 c.c.) and concentrated hydrochloric acid (2 c.c.) for an hour at 100°. After addition of boiling water (50 c.c.) and cooling, pale yellow slender needles separated, which, after recrystallisation from alcohol, yielded light yellow prisms, m. p. 202—203° (Found : C, 63·5; H, 5·2. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·0%). Rao and Seshadri (*J.*, 1947, 771) record very pale yellow, rectangular plates and prisms, m. p. 200—201°, for this compound. The flavone is insoluble in sodium hydrogen carbonate solution, soluble in sodium carbonate and sodium hydroxide solutions with bright yellow colours, and readily soluble in concentrated hydrochloric or sulphuric acid with an intense yellow colour. No colour is given with alcoholic ferric chloride solution, but a red colour when reduced both with magnesium, hydrochloric acid, and alcohol and with sodium amalgam and alcohol after acidification. The acetate, prepared as previously from 30 mg., after repeated crystallisation from alcohol, formed colourless needles, m. p. 179·5° (Found : C, 63·4; H, 5·1. Calc. for $C_{21}H_{20}O_8$: C, 63·0; H, 5·0%). Rao and Seshadri (*loc. cit.*) record m. p. 178—180°.

5 : 7 : 8-Trihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (2·7 g., 1 mol.) was added to a solution of potassium hydroxide (2·7 g.) in water (450 c.c.). Complete dissolution did not occur owing to the limited solubility of this flavone in aqueous alkali. Potassium persulphate (3·5 g., 2 mols.), dissolved in water (100 c.c.), was added dropwise during 1 hour. It was found in a trial run that warming to complete dissolution after the addition of persulphate gave a better yield than did adding pyridine. The mixture was therefore heated to 53°, solution then being nearly complete, and set aside overnight. After removal of a yellow sediment (0·4 g.), the filtrate was acidified, filtered, and extracted with ether. The aqueous residue was then treated with sodium sulphite (6 g.) and concentrated hydrochloric acid (50 c.c.) on the water-bath for 1½ hours. A brown solid (0·4 g.) separated, which, after repeated crystallisation from alcohol (charcoal), formed deep yellow needles, m. p. 198—199° (Found : C, 66·0; H, 5·2. $C_{24}H_{20}O_8$ requires C, 66·1; H, 4·6%). No further product could be obtained from the residue by continuous extraction with ether. The *flavone* is insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, giving a yellowish-brown colour which rapidly fades to a colourless solution with black insoluble particles, the solution finally changing to a faint blue. In a buffer at pH 9·8 it gives a bright yellow solution which slowly fades. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. A dark brown colour is given with alcoholic ferric chloride solution, and a reddish-brown colour on reduction with magnesium, hydrochloric acid, and alcohol. Only a weak yellow colour is produced by sodium amalgam and alcohol followed by acidification.

*5-Hydroxy-4′-benzyloxy-*3 : 7 : 8 : 3′*-tetramethoxyflavone*.—The preceding flavone (185 mg., 1 mol.), dissolved in dry acetone, was heated under reflux for 6 hours with methyl sulphate (0·09 c.c., 2·2 mols.) and anhydrous potassium carbonate. The acetone solution and washings of the insoluble salts were concentrated and acidified with one drop of concentrated hydrochloric acid. On cooling, yellow needles separated which, after recrystallisation from alcohol, had m. p. 170—171° (33 mg.) (Found: C, 67·1; H, 5·3. $C_{26}H_{24}O_8$ requires C, 67·2; H, 5·2%). The *flavone* is insoluble in 10% sodium hydroxide solution or concentrated hydrochloric acid, but soluble in concentrated sulphuric acid with an intense yellow colour. A green colour is given with alcoholic ferric chloride solution, and a strong pink colour with magnesium, hydrochloric acid, and alcohol; reduction with sodium amalgam and alcohol followed by acidification produces a violet colour.

5 : 4′*-Dihydroxy-*3 : 7 : 8 : 3′*-tetramethoxyflavone* (*Ternatin*).—The preceding flavone (25 mg.) was hydrolysed with glacial acetic acid (1 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for one hour at 100°. On pouring the solution into boiling water (10 c.c.), pale yellow needles (18 mg.) separated on cooling, which, after recrystallisation from alcohol, had m. p. 210·5—212·5°, undepressed by a specimen of natural ternatin, m. p. 210—212°. The ultra-violet and visible spectra of the synthetic and the natural specimen were also identical (forthcoming communication). The synthetic product was also insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, and gave a green colour with ferric chloride solution. The acetate, prepared as previously from 6 mg., on crystallisation from alcohol, formed colourless needles, m. p. 168—169°, which did not depress the m. p. of a sample prepared from natural sources. The synthetic acetate, like that from a natural sample, is photosensitive, becoming orange on exposure to light (Found, on a sample crystallised from both sources: C, 60·8; H, 4·8. Calc. for $C_{23}H_{22}O_{10}$: C, 60·3; H, 4·8%).

The analyses are by Drs. Weiler and Strauss, Oxford. We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for grants, and one of us (R. H. L.) for a Research Scholarship.

AUCKLAND UNIVERSITY COLLEGE,
AUCKLAND, NEW ZEALAND.

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176. *The Chemistry of the* Mitragyna *Genus. Part I.*

By G. M. BADGER, J. W. COOK, and P. A. ONGLEY.

The alkaloids of the leaves and bark of several species of *Mitragyna* have been examined as a preliminary to a more intensive chemical study of compounds of this class. Rotundifoline has been extracted from the leaves, and rhyncophylline from the bark, of *M. ciliata*. The identity of rhyncophylline with mitrinermine, suggested by Raymond-Hamet and supported by Barger *et al.* but disputed by Millat, has been established. A new phenolic alkaloid, *mitragynol*, has been isolated from *M. rotundifolia*; its methyl ether has been shown to be identical with dihydrorotundifoline. The hitherto unknown *dextro*-form of mitraphylline has been isolated from *M. rubrostipulaceæ*. Evidence has been obtained that the base, $C_9H_{13}N$, obtained by Barger *et al.* by selenium dehydrogenation of rotundifoline is 3 : 4-diethylpyridine.

Quinovic acid has been extracted from both leaves and bark of several species of *Mitragyna*, and a sterol from the bark of *M. inermis* has been identified as *β*-sitosterol.

THIS communication is concerned mainly with the isolation and characterisation of the alkaloids from several species of *Mitragyna*, preliminary to a structural study of this group of alkaloids. The genus *Mitragyna* occurs in the natural order Rubiaceæ, which has provided the cinchona alkaloids and also yohimbine. The isolation of several *Mitragyna* alkaloids has already been reported by other workers. These alkaloids include: mitragynine, probably $C_{22}H_{30}O_4N_2$; mitraphylline (rubradinine), $C_{21}H_{26}O_4N_2$; mitraspecine, $C_{23}H_{36}O_5N_2$ (?); mitraversine, $C_{22}H_{26}O_4N_2$ (?); rhyncophylline, $C_{22}H_{28}O_4N_2$; and rotundifoline, $C_{22}H_{26}O_5N_2$. Their structures have been very little investigated although it is known that only one of the two nitrogen atoms is basic and it has been suggested that the other is in an indole ring. Possibly a carboline system is present (cf. Ing and Raison, *J.*, 1939, 986). In some of these alkaloids two of the oxygen atoms have been shown to be present in a carbomethoxyl group and one in a methoxyl group, but the remaining oxygen atoms have not been characterised.

" Mitrinermine " was isolated from *M. inermis* O. Kuntze by Raymond-Hamet and Millat (*Compt. rend.*, 1934, **199**, 587) and also from *M. stipulosa* O. Kuntze by the same workers (*J. Pharm. Chim.*, 1934, **20**, 577). We have now isolated it from the bark of *M. ciliata* and have established its identity by melting-point comparisons of the free base, its chloroaurate, and its chloroplatinate. It was suggested by Raymond-Hamet (*Compt. rend.*, 1936, **203**, 1383) that "mitrinermine" might be identical with rhyncophylline, which Kondo, Fukuda, and Tomita (*J. Pharm. Soc. Japan*, 1928, **48**, 321) had isolated from *Ourouparia rhyncophylla* (N. O. Rubiaceæ). This view was supported by toxicity experiments with samples of "mitrinermine" and rhyncophylline (Raymond-Hamet, *Compt. rend. Soc. Biol.*, 1938, **128**, 777) and was accepted by Barger, Dyer, and Sargent (*J. Org. Chem.*, 1939, **4**, 418) who isolated from the leaves of *M. rotundifolia* (Roxb.) O. Kuntze an alkaloid which was indistinguishable from authentic samples of "mitrinermine" and rhyncophylline, and also a new alkaloid, rotundifoline. The identity of "mitrinermine" and rhyncophylline was later challenged by Millat (*Ann. Pharm. franç.*, 1946, **4**, 27) on the ground of supposed differences in elementary composition, colour reactions with Fröhde's reagent, melting point, and specific rotation. The analytical figures of Akamatsu (*Nagasaki Igakkai Zasshi*, 1928, **6**, 333; cf. Millat, *loc. cit.*) do, in fact, suggest $C_{21}H_{28}O_4N_2$ as the formula for rhyncophylline, but those of Kondo (*loc. cit.*) are in agreement with $C_{22}H_{28}O_4N_2$, which is also the formula for "mitrinermine." Moreover, M. Raymond-Hamet has informed us that the colour normally given by rhyncophylline with Fröhde's reagent is due to an impurity. Also, the melting point of mitrinermine is not 203°, as cited by Millat, but 215—216° (Raymond-Hamet and Millat, *loc. cit.*; *Bull. Sci. Pharmacol.*, 1934, **41**, 533), which agrees with that of rhyncophylline. We have carried out mixed melting point determinations with mitrinermine isolated from *M. inermis* and the alkaloid isolated by Barger, Dyer, and Sargent (*loc. cit.*) from *M. rotundifolia* and regarded by them as rhyncophylline. There was no depression, and this applies also to the chloroaurates and chloroplatinates prepared from the alkaloid from each source. The figures for these were in good agreement with those cited by Kondo for the rhyncophylline derivatives. Finally, a careful comparison of the specific rotation of the alkaloid from each source, using light of different wave-lengths, failed to show any differences. It is noteworthy that the specific rotations of this and other *Mitragyna* alkaloids vary very greatly with concentration.

Barger *et al.* (*loc. cit.*) described some degradation experiments with rhyncophylline. We have now obtained evidence that its molecule contains one double bond. Its solution in chloroform decolorises bromine without liberation of hydrogen bromide although it gives no colour with tetranitromethane. Hydrogenation in acetic acid solution did not take place with a palladium catalyst, but with Adams's platinum catalyst there was absorption of one molecular proportion of hydrogen.

From the leaves of *M. rotundifolia* Barger *et al.* (*loc. cit.*) isolated, not only rhyncophylline, but also rotundifoline. We have simplified the separation of these two alkaloids and have also isolated rotundifoline from the leaves of *M. ciliata*, from the bark of which we have obtained rhyncophylline. Although it is unusual for two alkaloids to occur, one in the bark and the other in the leaves of the same species, this is by no means unknown. The co-existence of the two alkaoids in both *M. ciliata* and *M. rotundifolia* suggests a close chemical relationship and it may be that rotundifoline is an oxidation product of rhyncophylline.

By the selenium dehydrogenation of rotundifoline Barger *et al.* (*loc. cit.*) obtained a mixture of bases from which they isolated a picrate, m. p. 134—135°, of composition indicating a base $C_9H_{13}N$. Witkop (*J. Amer. Chem. Soc.*, 1948, **70**, 3713) has shown that this base is not 2 : 4-dimethyl-3-ethylpyridine, the picrate of which has a similar melting point. Koenigs and Bernhart (*Ber.*, 1905, **38**, 3049) give m. p. 139° for the picrate of 3 : 4-diethylpyridine, which has the same composition, and we undertook some preliminary experiments on the synthesis of this base. Recently Karrer and Enslin (*Helv. Chim. Acta*, 1949, **32**, 1390) have described the formation of 3 : 4-diethylpyridine by degradation of corynanthyrine, which is itself formed by selenium dehydrogenation of the alkaloid corynantheine. We were fortunate enough to obtain a sample of Barger's picrate, given to us by Dr. Klyne, and found that its melting point was not depressed by admixture with synthetic 3 : 4-diethylpyridine picrate for a sample of which we are indebted to Professor Karrer. It would seem, therefore, that 3 : 4-diethylpyridine is a product of selenium dehydrogenation of rotundifoline.

With bromine in chloroform solution and with palladium and platinum catalysts in acetic acid, rotundifoline behaved exactly like rhyncophylline. *Dihydrorotundifoline*, obtained by hydrogenation with Adams's platinum catalyst, was isolated and characterised, and *rotundifoline dibromide* was also prepared. Rotundifoline gave a deep yellow colour with tetranitromethane, and also gave colours with Mandelin's and Erdmann's reagents but not with Fröhde's reagent. The similarity of the rotations of rotundifoline and dihydrorotundifoline suggests that the ethylenic bond in the former is unconjugated and this was confirmed by comparison of the absorption spectra, for which we are indebted to Dr. E. Clar who found that the two compounds gave almost identical spectra.

Through the good offices of Dr. W. Klyne, and the kindness of Drs. Dyer and Sargent, we have been able to examine some of the crude phenolic alkaloid extracted by Barger, Dyer, and Sargent (*loc. cit.*) from the leaves of *M. rotundifolia*. This was purified by chromatography on alumina and yielded a new crystalline alkaloid, *mitragynol*, $C_{21}H_{26}O_5N_2$, characterised as its *hydrochloride*. The colour reactions of mitragynol with Erdmann's, Fröhde's, and Mandelin's reagents were similar to those of rhyncophylline and rotundifoline, and ferric chloride in ether gave a red colour. Tetranitromethane gave an orange colour with mitragynol, but there was no other evidence of unsaturation; the compound did not decolorise bromine in chloroform, nor did it absorb hydrogen over Adams's platinum catalyst in acetic acid. Mitragynol appeared to have the character of a phenol, for it was soluble in sodium hydroxide solution, but not in sodium hydrogen carbonate solution, and gave a reddish-brown colour with ethanolic ferric chloride. By treatment with diazomethane mitragynol was converted into methylmitragynol which was insoluble in alkali and gave very little intensification of colour with ethanolic ferric chloride. Methylmitragynol proved to be identical with dihydrorotundifoline.

Differentiation between rotundifoline and dihydrorotundifoline was not easy, as the two compounds had almost the same melting point and there was no depression on mixing them. This applied also to the chloroplatinates and we did not succeed in preparing other crystalline salts. However, Barger's specimen of rotundifoline, isolated from *M. rotundifolia*, absorbed hydrogen equivalent to one double bond and also gave a very dark red colour with ferric chloride in ether. These characteristics were likewise shown by the rotundifoline which we isolated from *M. ciliata*, but not by dihydrorotundifoline or methylmitragynol, which we regard as identical. Moreover, by treatment of the last two substances with bromine under conditions which led to the formation of a dibromide from rotundifoline, brominated products could not be isolated. Rotundifoline gave a permanent flocculent precipitate with antimony pentachloride in chloroform; dihydrorotundifoline and methylmitragynol gave only a temporary haziness with this reagent.

Methoxyl determinations on these compounds gave results for which an explanation cannot yet be given. The determinations were carried out by Pregl's micro-modification of the Zeisel method. Mitragynol gave a value indicating the presence of two methoxyl groups; methylmitragynol, which is apparently obtained by methylation of a phenolic or enolic hydroxyl group also gave a value corresponding with two methoxyl groups. This latter value accords with that quoted by Barger *et al.* (*loc. cit.*), which we have confirmed, for rotundifoline. These authors found no *N*-methyl in rotundifoline. It appears, therefore, that the action of diazomethane on mitragynol methylates an acidic hydroxyl group to give a methoxyl group which is not hydrolysed under the conditions of the Zeisel determination. An example of failure of a methoxy-compound to respond to this analytical treatment had already been encountered by Dr. R. Schoental in these laboratories, and her results are recorded in an appendix to this communication. In her case lack of solubility may be the explanation, but this cannot apply in the cases of rotundifoline and methylmitragynol (dihydrorotundifoline).*

Mitraphylline has been isolated from *M. rubrostipulaceæ* (*Adina rubrostipulata* K. Schumann) by Michiels (Michiels and Leroux, *Bull. Acad. roy. méd. Belg.*, 1925, **5**, 403; Michiels, *J. Pharm. Belg.*, 1935, **17**, 1049), by Denis (*Bull. Acad. roy. Belg.*, 1937, **23**, 174) who named it rubradinine, and by Raymond-Hamet (*Bull. Sci. pharmacol.*, 1939, **46**, 327); Michiels (*J. Pharm. Belg.*, 1931, **13**, 719) also isolated it from *M. stipulosa* (*M. macrophylla*). We have examined several samples of *M. rubrostipulaceæ* and have isolated *lævo*-mitraphylline from the leaves and *dextro*-mitraphylline from the bark. Michiels (*J. Pharm. Belg.*, 1931, **13**, 719) has reported " inactive " mitraphylline, and we also have isolated material which showed no optical rotation. Mitraphylline gave a yellow colour with tetranitromethane and formed a *dibromide*. It absorbed one molecule of hydrogen when treated in acetic acid with hydrogen and a palladium catalyst. With Adams's platinum catalyst one molecular proportion of hydrogen was rapidly absorbed, and two further molecular proportions were slowly taken up.

During extractions of the alkaloids from various species of *Mitragyna* we have observed the presence of a triterpene acid in considerable amount. This acid was isolated from the bark of *M. inermis* and from both bark and leaves of *M. ciliata* and *M. rubrostipulaceae*. In every case it has been identified as quinovic acid, long known as a constituent of cinchona bark (natural order Rubiaceæ) (Liebermann, *Ber.*, 1884, **17**, 868) and more recently found in *Zygophyllum coccineum* L., an Egyptian plant of the natural order Zygophyllaceæ (Soliman, *J.*, 1939, 1760).

We have also examined a sample of sterol kindly given to us by M. Raymond-Hamet, who isolated it from the bark of *M. inermis*. After purification, determinations of the melting points and specific rotations of the sterol, its acetate, and its 3 : 5-dinitrobenzoate indicated that the sterol was β-sitosterol (cf. Ichiba, *Inst. Phys. Chem. Res., Tokyo*, 1935, **28**, 112; Simpson and Williams, *J.*, 1937, 733), and this view was supported by direct comparison with authentic specimens of β-sitosterol and its corresponding derivatives (Cook and Paige, *J.*, 1944, 336).

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* See also Nunn and Rapson, *J.*, 1949, 3155.

EXPERIMENTAL.

Rhyncophylline.—A mixture of finely ground *M. inermis* bark (15 kg.) and calcium oxide (5 kg.) was moistened, air-dried at 40°, and then extracted with hot chloroform in a continuous extractor until a sample of extract no longer gave a precipitate with Mayer's reagent. After removal of the chloroform the residual paste was extracted with 3% hydrochloric acid until the residue was free from basic material. The alkaloid (2 g.) was then precipitated by addition of concentrated ammonia solution. Rhyncophylline then crystallised from methanol in small colourless prisms, m. p. 212—213°, not depressed by admixture with specimens supplied by Dr. Klyne, extracted from both *M. inermis* and *M. rotundifolia*. The chloroplatinate formed orange prisms (from methanol) which decomposed at 236° (Kondo *et al.*, *loc. cit.*, give 238° for the decomposition point of the chloroplatinate of rhyncophylline). The chloroaurate melted at 132° and then decomposed at 155° (Kondo gives 134° and 155°, respectively).

Similar extraction of the bark (500 g.) of *M. ciliata* gave crystalline rhyncophylline (0·1 g.), m. p. 211°; its chloroplatinate decomposed at 236—237°, and its chloroaurate at 155—157°, after melting at 133°. Mixed-m. p. determinations showed no depressions.

A specimen of rhyncophylline extracted from *M. rotundifolia* by Barger, Dyer, and Sargent (*loc. cit.*) gave a chloroplatinate which formed orange prisms and decomposed at 235° after darkening (Found : C, 44·6; H, 5·0; Pt, 16·2. Calc. for $C_{44}H_{58}O_8N_4Cl_6Pt$: C, 44·8; H, 5·0; Pt, 16·55%), and a chloroaurate which melted at 132° and then decomposed at 155°. These values also showed no depressions when the specimens were mixed with corresponding compounds of rhyncophylline prepared from *M. inermis.*

Optical Rotations.—The following measurements, made with chloroform solutions at 19° ($l = 1$) serve to confirm the identity of the alkaloid (*I*) from *M. inermis* with that (*R*) isolated by Barger *et al.* (*loc. cit.*) from *M. rotundifolia :*

Sample.	Concn.	Wave-length of source :	$[\alpha]$. 7000.	6500.	5900.	5500.	5000.
R	5·30		—	—	−6·0°	—	—
R	2·35		—	−12·6°	−14·3	−15·3°	−16·6°
I	2·26		−12·6°	−14·6	−15·7	−17·5	−18·7
R	1·00		−16·0	−18·0	−22·0	−28·0	−36·0
I	1·13		−17·7	−20·4	−23·0	−28·3	−37·2

Rotations were also measured of solutions in 2N-hydrochloric acid at 19° ($l = 1$) as follows (concentrations given as weight of base in 100 c.c. of acid) :

	Concn.	7000.	6500.	5900.	5500.	5250.	5000.
R	1·50	+1·0°	+1·7°	+3·3°	+4·7°	+6·7°	+8·3°
I	1·50	+1·0	+1·7	+2·7	+4·0	+6·0	+8·0

Specific rotations given in the literature for rhyncophylline are $[\alpha]_D^{13}$ −14·7° (Kondo *et al.*) and $[\alpha]_D^{15}$ −14·5° (*c*, 2·5 in chloroform) (Barger *et al.*). For " mitrinermine," Raymond-Hamet and Millat (*J. Pharm. Chim.*, 1934, **20**, 577) give $[\alpha]$ −23·0° (*c*, 1·45), −23·1° (*c*, 1·51), −26·4° (*c*, 1·45), and −26·5° (*c*, 1·19) (all in chloroform).

Rotundifoline.—A mixture of the minced leaves of *M. ciliata* (500 g.) and calcium oxide (100 g.) was moistened, dried, and extracted for 16 hours with hot chloroform. The extracted alkaloid was crystallised from ethanol (yield, 0·8 g.) and had m. p. 233°, not depressed on admixture with an authentic specimen of the rotundifoline of Barger *et al.* (*loc. cit.*), who give m. p. 233—234°. The observation that rotundifoline is sparingly soluble in chlorobenzene whereas rhyncophylline is easily soluble made it possible to effect a ready separation of these two alkaloids from the crude mixture obtained from *M. rotundifolia.* Polarimetric comparison (in chloroform at 21°; $l = 1$) of the alkaloid from *M. ciliata* (*C*) with Barger's rotundifoline (*Ro*) confirmed their identity.

	Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
C	2·10	+85·7°	+98·6°	+123·5°	+145·2°	+163·9°	+184·8°	+217·6°
Ro	2·10	+84·8	+97·6	+122·4	+143·8	+162·4	+184·3	+214·3

[Barger *et al.*(*loc. cit.*) give $[\alpha]_D^{15}$ + 124° (*c*, 2·14 in chloroform)].

The following rotations were observed for solutions of rotundifoline in 2N-hydrochloric acid at 21° (*c*, 2·48 g. per 100 c.c.; $l = 1$) :

7000.	6500.	5900.	5500.	5250.	5000.	4750.
+44·8°	+48·4°	+60·9°	+70·6°	+79·0°	+90·7°	+109·6°

With Mandelin's reagent rotundifoline gave a brown colour which became olive-green on storage; with Fröhde's reagent there was no colour, and with Erdmann's reagent no immediate colour but a light brown colour developed on storage. A methoxyl determination was carried out on the sample of Barger's rotundifoline supplied by Dr. Klyne (Found : OMe, 16·2. Calc. for $C_{22}H_{28}O_5N_2$: 2OMe, 15·6%). The *chloroplatinate* of rotundifoline had m. p. 232—234° (decomp.) (Found: C, 43·4; H, 5·1. $C_{44}H_{58}O_{10}N_4Cl_6Pt$ requires C, 43·7; H, 4·6%).

Rotundifoline was not hydrogenated in ethanolic solution with Adams's platinum catalyst or with Raney nickel at 75°/30 atmospheres. Attempted micro-hydrogenation in acetic acid with palladium-black was likewise unsuccessful, but with Adams's platinum catalyst in acetic acid one molecular proportion of hydrogen was absorbed. Repetition on a macro-scale led to the isolation of *dihydrorotundifoline*, which formed colourless needles (from methanol), m. p. 233°, not depressed on admixture with rotundifoline (Found: C, 65·6; H, 7·3. $C_{22}H_{28}O_5N_2$ requires C, 66·0; H, 7·1%). The rotation of dihydrorotundifoline in chloroform at 21° (*c*, 2·41) was as follows:

7000.	6500.	5900.	5500.	5250.	5000.	4750.
+96·7°	+103·7°	+123·7°	+147·7°	+163·5°	+189·6°	+220·3°

The chloroplatinate of dihydrorotundifoline had m. p. 224—226° (from methanol), not depressed on admixture with the chloroplatinate of methylmitragynol described below.

Rotundifoline was treated with bromine in chloroform at room temperature until no more was taken up, and the product was heated under reflux with acetone to reduce perbromide. The resulting *dibromide* was further purified by repeated dissolution in dilute hydrochloric acid and reprecipitation with aqueous ammonia. It formed an amorphous powder, m. p. 215° (Found: C, 47·2; H, 4·8; Br, 28·8. $C_{22}H_{26}O_5N_2Br_2$ requires C, 47·3; H, 4·7; Br, 28·6%).

3 : 4-*Diethylpyridine Picrate*.—A sample of the picrate of the base formed by selenium dehydrogenation of rotundifoline (Barger, Dyer, and Sargent, *loc. cit.*), given to us by Dr. Klyne, had micro-m. p. 131—133°. Its m. p. was not depressed when the salt was mixed with a specimen of 3 : 4-diethylpyridine picrate (micro-m. p., 134—136°) presented by Professor Karrer.

Mitragynol.—The pale brown amorphous phenolic alkaloid (10 g.) from *M. rotundifolia* (Barger *et al.*, *loc. cit.*), for which we are indebted to Dr. Klyne, was dissolved in chloroform (100 c.c.), and its solution passed through a column of alumina (2 × 12 cm.), previously saturated with benzene. The column was eluted with chloroform (150 c.c.). Evaporation of the solvent gave an amorphous mass which crystallised on storage with methanol (yield of colourless crystals, 5·8 g.). *Mitragynol* crystallised from methanol in colourless transparent needles which became opaque on storage. After being dried in a vacuum, it had m. p. *ca.* 130°, depending on the rate of heating (Found: C, 65·3; H, 6·9; N, 7·1; OMe, 15·45, 14·8. $C_{21}H_{26}O_5N_2$ requires C, 65·25; H, 6·8; N, 7·25; 2OMe, 16·0%). Specific rotations at different concentrations and wave-lengths were:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.
4·24	+2·8°	+1·4°	+0·5°	−0·5°	−0·7°	−2·1°
2·12	−2·8	−3·8	−4·7	−5·2	−6·6	−8·0
1·06	−5·7	−7·6	−8·7	−10·4	−12·3	−13·2

The *hydrochloride*, prepared in aqueous solution and recrystallised from water, formed colourless needles, m. p. 212—216° (Found: C, 59·6; H, 6·2; N, 6 8. $C_{21}H_{27}O_5N_2Cl$ requires C, 59·6; H, 6·4; N, 6·6%). The analytical specimen was dried at 100° *in vacuo*. Specific rotations in aqueous solution at 21° (*c*, 3·75; *l* = 1) were:

7000.	6500.	5900.	5500.	5250.	5000.	4750.
−30·9°	−34·9°	−42·9°	−51·4°	−57·1°	−64·3°	−71·4°

With Mandelin's reagent mitragynol gave a transient brown colour, changing to olive-green; with Fröhde's reagent there was no colour and with Erdmann's reagent a very faint brown colour on storage. Tetranitromethane gave an orange colour. Mitragynol gave no sparingly soluble chloroplatinate and did not absorb hydrogen in acetic acid over Adams's platinum catalyst.

For methylation, a solution of mitragynol (0·6 g.) in ether and methanol was set aside overnight with excess of ethereal diazomethane. The residue obtained by evaporation was recrystallised from methanol, giving colourless needles (0·46 g.), m. p. 232—233°, not depressed on admixture with dihydrorotundifoline (above) (Found: C, 65·8; H, 6·9; OMe, 15·4. Calc. for $C_{22}H_{28}O_5N_2$: C, 66·0; H, 7·1; OMe, 15·6%). Identity was confirmed by preparation of the *chloroplatinate*, which crystallised from ethanol in orange-yellow prisms, m. p. 224—226° (Found: C, 43·6; H, 5·1; Pt, 15·7. $C_{44}H_{58}O_{10}N_4Cl_6Pt$ requires C, 43·6; H, 4·8; Pt, 16·1%). The following rotations (in chloroform at 21°; *l* = 1) were observed with the dihydrorotundifoline (methylmitragynol) prepared in this way:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
3·28	+86·6°	+102·1°	+122·6°	+144·5°	+163·4°	+186·9°	+218·3°
1·64	+92·7	+109·7	+126·3	+151·2	+166·9	+194·5	+223·8
0·822	+88·0	+109·7	+128·0	+154·9	+178·0	+202·4	+225·5

Mitraphylline.—(*a*) Finely ground bark of *M. rubrostipulacea* (500 g.) was mixed with calcium oxide (125 g.), moistened, air-dried, and extracted for 16 hours with hot chloroform. The mitraphylline recovered from the extract formed long colourless needles, m. p. 262° (from methanol), and gave a picrate, m. p. 165° (Raymond-Hamet and Millat, *Bull. Sci. Pharmacol.*, 1935, **42**, 602, give m. p. varying between 258° and 267° for the alkaloid, and Denis, *loc. cit.*, gives m. p. 166° for the picrate). Specific rotations of the base in chloroform at 21° (*l* = 2) were:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750
1·96	+4·3°	+5·4°	+7·1°	+9·2°	+11·7°	+14·8°	+19·1°
0·98	+2·5	+3·5	+4·6	+5·6	+7·7	+10·2	+13·3

In 2N-hydrochloric acid at 21° ($l = 1$; concentrations in g. of base per 100 c.c.) the rotations were:

Concn.	7000.	6500.	5900.	5500.	5250.	5000.	4750.
2·70	+18·6°	+22·6°	+26·7°	+30·4°	+34·1°	+37·8°	+41·9°
1·35	+14·8	+17·8	+21·5	+28·9	+32·6	+36·3	+40·8

(*b*) Finely ground leaves of *M. rubrostipulaceæ* (500 g.), extracted similarly, gave the same alkaloid (2·5 g.), m. p. 261° alone or mixed with the sample described in the previous paragraph or with mitraphylline kindly given us by M. Raymond-Hamet. The picrate had m. p. 165°, not depressed by the picrate of the alkaloid from the bark A sample of leaves supplied about 6 months later gave only one-tenth of the amount of alkaloid for the same weight of leaves; this was lævorotatory, having $[\alpha]_D^{20}$ −7·4° (*c*, 1·20 in chloroform) (Found: C, 68·3; H, 7·0; N, 7·3; OMe, 8·5. Calc. for $C_{21}H_{26}O_4N_2$: C, 68·0; H, 7·0; N, 7·6; OMe, 8·4%). For mitraphylline in chloroform, Raymond-Hamet and Millat (*loc. cit.*) give $[\alpha]_D$ −7·7° (*c*, 3·9) and −5·8° (*c*, 1·2), Raymond-Hamet (*Bull. Sci. Pharmacol.*, 1939, **46**, 327) gives $[\alpha]_D^{18}$ −9·8° (*c*, 0·51) and Denis (*loc. cit.*) gives $[\alpha]_D$ −22·27° (*c*, 4·8), whereas Michiels and Delvaux (*J. Pharm. Belg.*, 1931, **13**, 719) describes mitraphylline as having zero rotation. More recently we also have extracted the alkaloid from about a hundredweight of bark and leaves of *M. rubrostipulaceæ* and have isolated optically inactive mitraphylline.

Microhydrogenation of mitraphylline in acetic acid over Adams's platinum catalyst led to absorption of 3 moles of hydrogen. The first molecule was taken up in 18 minutes, and the other two each required 40 minutes. Microhydrogenation over palladium-black led to absorption of one mole of hydrogen.

Treatment of mitraphylline with bromine in chloroform at room temperature gave an amorphous product which was heated under reflux with acetone to decompose perbromide and then purified by repeated solution in dilute hydrochloric acid and reprecipitation with aqueous ammonia. The dibromide, an amorphous powder, m. p. 195—198°, was converted into its *chloroplatinate* which formed small yellow leaflets (from methanol) and decomposed at 190° (Found: C, 34·4; H, 3·95; Pt, 12·5. $C_{42}H_{54}O_8N_4Cl_6Br_4Pt$ requires C, 34·3; H, 3·7; Pt, 13·3%).

Quinovic Acid.—The *M. inermis* bark from which the alkaloid had been extracted (above) was kept for 24 hours in 10% sodium carbonate solution (20 galls.), and then percolated with a further equal volume. The bark was pressed manually, and the combined extracts were treated with "Supercel" and then acidified with 15% hydrochloric acid. The filtered precipitate was re-dissolved in alkali and reprecipitated after filtration from the "Supercel." The crude acid was purified by repeated crystallisation from ethanol, with charcoal. The yield of almost pure acid was 50 g.

The pure acid formed colourless crystals (Found: C, 73·8, 74·1; H, 9·3, 9·4%; equiv., by titration, 240, 248, 249. Calc. for $C_{30}H_{46}O_5$: C, 74·0; H, 9·5%; equiv., 243), m. p. 298° (alone or mixed with an authentic specimen of quinovic acid kindly presented by Professor L. Ruzicka), $[\alpha]_D^{20}$ +99° (*c*, 2·48 in pyridine). For the potassium salt (concn. expressed as g. of acid in potassium carbonate solution), $[\alpha]_D^{19}$ = +89° (*c*, 0·98) (lit.: m. p. of quinovic acid, 298°; $[\alpha]_D^{16}$ of potassium salt, +87°).

The methyl ester, prepared with excess of ethereal diazomethane, formed colourless crystals (from light petroleum), m. p. 172—173°, not depressed in admixture with an authentic specimen of methyl quinovate. It had $[\alpha]_D^{19}$ +117·4° (*c*, 2·12 in chloroform) (lit.: m. p. 173—174°; $[\alpha]_D^{19}$ +115·2°, +116·8°, in chloroform).

The acetyl derivative, prepared by heating the acid with excess of acetic anhydride under reflux, crystallised from methanol in colourless needles, m. p. 281—282° (lit., 284°) (Found: C, 73·0, 72·8; H, 9·05, 9·2. Calc. for $C_{32}H_{48}O_6$: C, 72·6; H, 9·15%).

Quinovic acid was also isolated from both bark and leaves of *M. ciliata* and *M. rubrostipulaceæ*. The following constants were given by the various specimens, and in all cases mixed m. p.s with authentic samples were carried out. The specific rotations are for the potassium salt, in water.

	M. inermis	*M. ciliata*		*M. rubrostipulaceæ*	
Source:	bark.	bark.	leaves.	bark.	leaves.
M. p. of acid	298°	300°	298°	303°	301°
$[\alpha]_D^{20}$	+86	+87	+87	+43, +44	+86
M. p. of acetyl derivative	281—282°	280—281°	283°	284°	281—281·5°
M. p. of methyl ester	172—173°	172—173°	171—173°	171—173°	172—174°

β-Sitosterol from M. inermis.—A sample of a sterol obtained from benzene extracts of *M. inermis* bark, after removal of rhyncophylline, was presented to us by M. Raymond-Hamet. Repeated recrystallisation from methanol gave crystals of m. p. 134—135° and $[\alpha]_D^{20}$ −35·6° (*c*, 1·54 in chloroform). This sterol, which was unsaturated, was converted into its acetate by acetic anhydride in pyridine at room temperature, and into its 3 : 5-dinitrobenzoate by 3 : 5-dinitrobenzoyl chloride in boiling pyridine. The m. p.s of the sterol and its two derivatives were not depressed on admixture with β-sitosterol and the corresponding derivatives, isolated by Cook and Paige (*loc. cit.*) from *Calycanthus floridus*, and the satisfactory agreement between constants, given in the following table, confirms the identification of the sterol from *M. inermis* as β-sitosterol.

	Sterol from *M. inermis*.	β-Sitosterol.
M. p. of sterol	134—135°	137·5—138·5° [1]
$[\alpha]_D$ of sterol	−35·6	−34·0 [1]
M. p. of acetate	128°	126·5—127·5° [1]
$[\alpha]_D$ of acetate	−38·5 [2]	−34·7 [3]
M. p. of 3 : 5-dinitrobenzoate	203—204°	208—209° [1]
$[\alpha]_D$ of 3 : 5-dinitrobenzoate	−20·7 [4]	−21·7 [3]

[1] Cook and Paige's values (*loc. cit.*), *q.v.* for figures given by earlier workers. [2] *c*, 1·20 in chloroform at 21°. [3] Simpson and Williams, *J.*, 1937, 733. [4] *c*, 1·20 in chloroform at 20°.

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APPENDIX. By MISS R. SCHOENTAL.

In connection with a study of the metabolic oxidation products of some polycyclic aromatic hydrocarbons, specimens have been prepared of the dimethyl ethers of the anthraquinols formed by alkaline reduction of three anthraquinone derivatives. Unexpected difficulty was encountered in the analysis of 9 : 10-dimethoxy-1 : 2 : 5 : 6-dibenzanthracene. Three attempts (by Mr. J. M. L. Cameron) to estimate the methoxyl content by Pregl's micro-modification of the Zeisel method gave a zero value, although the compound should contain two methoxyl groups. There can be little doubt that the structure is correctly assigned, for it is supported by the method of preparation and the elementary analysis of the compound and its picrate; moreover, the ultra-violet absorption spectrum of the dimethoxy-compound resembles very closely that of 1 : 2 : 5 : 6-dibenzanthracene (Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 320), with a shift towards the region of longer wave-length, which amounted to 100 A. for the longest band. This failure to hydrolyse the dimethyl ether is possibly caused by steric hindrance, but the compound is very sparingly soluble and this may be a contributory factor. Two other compounds of similar structure gave somewhat low values for the methoxyl content, which however clearly indicated the presence of two methoxyl groups in each case.

For preparation of these dimethoxy-compounds, the appropriate quinone was heated with zinc dust, aqueous sodium hydroxide, and methyl sulphate, the alkali and methyl sulphate being added alternately in small portions until the alkaline solution was almost completely decolorised. The product was extracted with benzene and the strongly fluorescent benzene solution was purified by chromatography on alumina. The concentrated benzene eluates were treated with light petroleum.

9 : 10-*Dimethoxy*-1 : 2-*benzanthracene* formed colourless rhombic plates, m. p. 137—138° (Found : C, 83·35; H, 5·7; OMe, 19·3. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6; OMe, 21·5%) (cf. Berenblum and Schoental, *Cancer Res.*, 1943, **3**, 686). 9 : 10-Dimethoxy-1 : 2 : 7 : 8-dibenzanthracene could not be obtained crystalline, but formed a s-*trinitrobenzene* complex which crystallised from ethanol in orange-yellow needles, m. p. 157—158° (Found : C, 65·35; H, 3·85; N, 7·7; OMe, 9·9. $C_{30}H_{21}O_8N_3$ requires C, 65·3; H, 3·8; N, 7·6; OMe, 11·2%). 9 : 10-*Dimethoxy*-1 : 2 : 5 : 6-*dibenzanthracene* formed colourless rhombic crystals, m. p. 234—235·5° (Found : C, 85·3; H, 5·5. $C_{24}H_{18}O_2$ requires C, 85·2; H, 5·4%) ; its *dipicrate* crystallised from benzene in deep-red needles, m. p. 183—184° (decomp.) (Found : C, 54·2; H, 2·9; N, 10·5. $C_{36}H_{24}O_{16}N_6$ requires C, 54·3; H, 3·0; N, 10·55%) .

UNIVERSITY OF GLASGOW.

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177. *" Leaf Alcohol " and the Stereochemistry of the* cis- *and the* trans-n-*Hex*-3-*en*-1-*ols and* -n-*Pent*-3-*en*-1-*ols.*

By LESLIE CROMBIE and STANLEY H. HARPER.

The stereochemistry of " leaf alcohol " is examined. The compound is shown to be *cis*-hex-3-enol, thus confirming the suggestion of Stoll and Rouvé. Takei's assignment of the *trans*-configuration to it is mistakenly based on the properties of a synthetic hexenol, which is not the true stereoisomer of " leaf alcohol " and is probably not homogeneous. Authentic *trans*-hex-3-enol is described and certain melting-point anomalies are removed.

The infra-red absorption spectra of *cis*- and *trans*-hex-3-enol are examined and the preparation of *cis*- and *trans*-pent-3-enol is described.

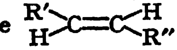
IN connection with our investigations of the sterochemistry of cinerone (Harper, *J.*, 1946, **892**; Crombie and Harper, *Nature*, 1949, **164**, 534), jasmone (Crombie and Harper, forthcoming publication), and related compounds, it became necessary to have available specimens of the *cis*- and the *trans*-form of pent-3-enol and of hex-3-enol. One stereochemical form of hex-3-enol is widely distrubuted in nature as " leaf alcohol " (Walbaum, *J. pr. Chem.*, 1917, [ii], **96**, 245; Takei, Sakato, Ono, and Kuroiwa, *J. Agric. Chem. Soc. Japan*, 1938, **14**, 709; Bohnsack, *Ber.*, 1941, **74**, 1575; 1942, **75**, 72; 1943, **76**, 564). It is usually isolated from green-tea oil or from the tailings of Japanese peppermint oil, in which it occurs as the phenylacetate, and is used in perfumery since it possesses the characteristic smell of green grass and leaves. Although its structure as a hex-3-enol is fully established, its stereochemical configuration has been the subject of dispute (Takei, *ibid.*, 1940, **73**, 950; Stoll and Rouvé, *ibid.*, p. 1358). The synthesis of " leaf alcohol " by Stoll and Rouvé (*Helv. Chim. Acta*, 1938, **21**, 1542), through the semihydrogenation of hex-3-ynol with a colloidal palladium catalyst, strongly favoured the *cis*-configuration. This was further supported by the presence of bands at 1267 and 1655 cm.$^{-1}$ in its Raman spectrum (Ruzicka, Schinz, and Susz, *ibid.*, 1944, **27**, 1561; cf. Grédy, *Bull. Soc. chim.*, 1935, [v], **3**, 1101). However an isomeric sharper-smelling hexenol had been prepared by Ruzicka and Schinz (*Helv. Chim. Acta*, 1934, **17**, 1602) and by Takei, Imaki, and Tada (*Ber.*, 1935, **68**, 953) by Bouveault–Blanc reduction of ethyl sorbate, which was accepted as the stereoisomer of " leaf alcohol." The derivatives of this hexenol melted at lower temperatures than those of " leaf alcohol " (see the table; but for a more comprehensive list see Takei, Sakato, Ono, and Kuroiwa, *loc. cit.*), a fact which led Takei to reject the *trans*-configuration for the former and to regard it as the *cis*-, " leaf alcohol " becoming the *trans*-isomer.

Since the Bouveault–Blanc reduction of ethyl sorbate gave a poor yield we have prepared trans-*hex-3-enol* by the lithium aluminium hydride reduction of *trans*-hex-2-enoic acid.* This acid was made by the Knoevenagel condensation of *n*-butaldehyde with malonic acid, using triethanolamine as catalyst (Boxer and Linstead, *J.*, 1931, 740; Linstead, Noble, and Boorman, *J.*, 1933, 557). It is reasonable to assume that this reaction gives a *trans*-acid since Lane, Fentress, and Sherwood (*J. Amer. Chem. Soc.*, 1944, **66**, 545) prepared a pent-2-enoic acid from crotyl chloride, which from the conditions of its formation has the *trans*-configuration, and this was identical with the pent-2-enoic acid prepared by the Knoevenagel condensation of propaldehyde (Linstead, Noble, and Boorman, *loc. cit.*). It is therefore considered that this hex-2-enoic acid and the hex-3-enol prepared from it have the *trans*-configuration. This conclusion has been confirmed by Dr. F. Sondheimer (private communication; succeeding paper) who has obtained an identical hexenol by the reduction of hex-3-ynol with sodium in liquid ammonia, a process that is known to give the pure *trans*-ethenoid product (Campbell and Eby, *ibid.*, 1941, **63**, 216, 2683; Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 90; Greenlee and Fernelius, *J. Amer. Chem. Soc.*, 1942, **64**, 2505).

This *trans*-hex-3-enol was clearly different from Ruzicka and Schinz's hexenol for it had a powerful but pleasant chrysanthemum-like odour and its derivatives melted at higher temperatures (see the table). The 1-naphthylurethane of the alcohol prepared by the Bouveault–Blanc reduction depressed both the melting point of the 1-*naphthylurethane* of our *trans*-hex-3-enol and that of " leaf alcohol." The identity of Ruzicka and Schinz's hexenol is not certain, but it may be a mixture of hex-3-enols and hex-4-enols, for the derivative melted rather unsharply. It is relevant that Goldberg and Linstead (*J.*, 1928, 2343) showed that sodium amalgam reduction of sorbic acid gave a mixture of hex-2-enoic and hex-3-enoic acids (" hydrosorbic acid "), which had previously been regarded as a homogeneous substance. Furthermore, Fischer and Wiedmann (*Annalen*, 1936, **522**, 1) state that reduction of sorbaldehyde with sodium in ethanol gives a mixture of hex-3-enol (~66%) and hex-4-enol (~33%).

Although the melting points of the 1-naphthylurethane and 3 : 5-*dinitrobenzoate* of *trans*-hex-3-enol were very close to those of the corresponding derivatives of " leaf alcohol," on admixture large depressions were observed. The p-*nitrophenylurethane* and the p-*diphenylylurethane* of *trans*-hex-3-enol, however, melted at higher temperatures than the corresponding derivatives of " leaf alcohol." " Leaf alcohol " is clearly not *trans*-hex-3-enol. Furthermore these melting points invalidate Takei's argument and there is no doubt that from the method of synthesis, the Raman spectrum, and by exclusion " leaf alcohol " is *cis*-hex-3-enol.

We have examined the tailings from the distillation of Brazilian peppermint oil (*Mentha Arvensis*) as a likely source of " leaf alcohol," although we are not aware of its presence having been previously recorded. Distillation gave fractions containing ester and the richest was hydrolysed to yield an exceptionally pure specimen of " leaf alcohol." The steam-volatile oily acid failed to crystallise when seeded with phenylacetic acid, from which it would appear as if " leaf alcohol " is not present as the phenylacetate in Brazilian peppermint oil.

The infra-red spectra of few *cis–trans* pairs of olefinic hydrocarbons have been measured, but it is now generally accepted that an absorption band at 10·3 μ. is due to the flapping vibrations of the hydrogen atoms about a *trans*-double bond of the type  ${}^{R'}_{H}\!\!>C{=}C\!\!<^{H}_{R''}$,

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* Following current Journal practice the carboxyl group is not numbered in this and other acids.

Properties of cis- *and* trans-*hex*-3-*enol and* -*pent*-3-*enol*.

		" Leaf Alcohol." *cis*-.	Product from LiAlH$_4$ reduction. *trans*-.	Product from Bouveault–Blanc reduction.
Hex-3-enol	B. p.	66—67°/19 mm.	52—53°/9 mm.	59—60°/12 mm.*
	$n_{\rm D}^{20}$	1·4384	1·4374	1·4376
1-Naphthylurethane	M. p.	69—70°	69—70°	61—63°
3 : 5-Dinitrobenzoate......	M. p.	49°	47—48°	28°
p-Nitrophenylurethane ...	M. p.	72·5—73·5°	84—85°	—
p-Diphenylylurethane ...	M. p.	91·0—91·5°	99·0—99·5°	—

		cis-.	*trans*-.
Pent-3-enol	B. p.	139—141°	136—137·5°
	$n_{\rm D}^{20}$	1·4386	1·4340
1-Naphthylurethane	M. p.	88—89°	93°

* Data taken from Ruzicka, Schinz, and Susz (*loc. cit.*) and from Takei, Imaki, and Tada (*loc. cit.*).

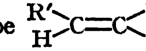
(cf. Rasmussen, Brattain, and Zucco, *J. Chem. Physics*, 1947, **15**, 135). There is some evidence too that an absorption maximum at 14 μ. in an olefinic hydrocarbon is to be associated with a *cis*-double bond of the type  $\overset{R'}{\underset{H}{}}\!\!>\!C{=}C\!<\!\overset{R''}{\underset{H}{}}$ (Anderson and Seyfried, *Analyt. Chem.*, 1948, **20**, 998; Hall and Mikos, *ibid.*, 1949, **21**, 422; Hampton, *ibid.*, p. 923). However, information on the infra-red spectra of olefinic *cis–trans* pairs other than hydrocarbons is very sparse. Elaidic acid (*trans*-) has a strong band at 10·3 μ. which is almost absent in oleic acid (*cis*-), and this band is also present in the spectrum of vaccenic acid (*trans*-). Both oleic and elaidic acid show absorption at 13·8—13·9 μ. (Rao and Daubert, *J. Amer. Chem. Soc.*, 1948, **70**, 1102). The infra-red spectra of *cis*- and *trans*-hex-3-enol therefore seemed of interest and were kindly determined by Miss I. M. Friedmann (see Figs. 1 and 2). The hydroxyl band at 9·5 μ. is strongly in evidence in both spectra, but the *trans*-alcohol shows a strong band at 10·3 μ. which is of very low intensity in the spectrum of the *cis*-alcohol, whereas the intensity of absorption at 13·9 μ. is markedly higher for the latter. These observations fall into line with the results quoted above and provide further evidence that " leaf alcohol " has the *cis*-configuration. Corresponding with the disappearance of the 10·3 μ. band characteristic of the *trans*-alcohol we find that a new band appears at 11·5 μ. in the spectrum of the *cis*-alcohol. There are also other minor differences between the two spectra. Observation of the bands at 10·3 μ., 11·5 μ., and 13·9 μ. may therefore be of considerable assistance in the assignment of geometrical configurations to compounds of the type CH$_2$R·CH:CH·CH$_2$R′, where R and R′ may be other than alkyl groups.

FIG. 1.

cis-*Hex*-3-*enol* (*natural*).

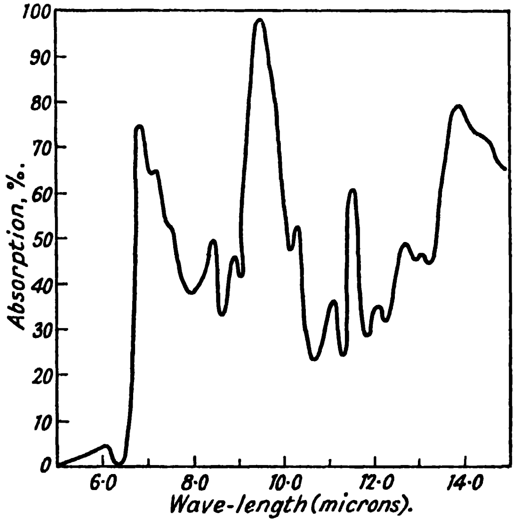
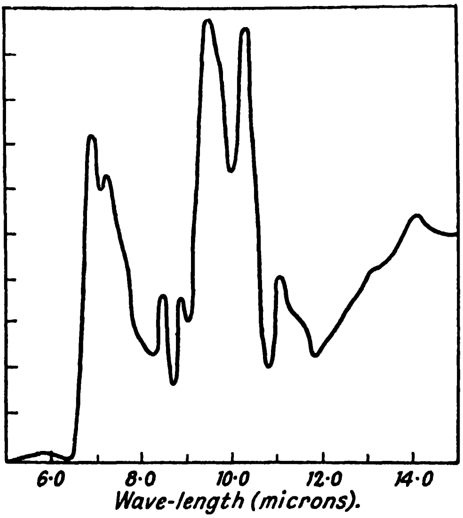


FIG. 2.

trans-*Hex*-3-*enol*.



Three preparations of pent-3-enol have been described in the literature. Goethals (*Natuurwetensch. Tijds.*, **1937**, **19**, 184; *Bull. Acad. roy. Belg.*, **1937**, [v], **23**, 721; *Bull. Soc. chim. Belg.*, **1937**, **46**, 409) attempted to prepare pent-3-enol by the Bouveault–Blanc reduction of ethyl pent-2-enoate but even under the best conditions the product was a mixture containing some 25% of *n*-amyl alcohol. From the Raman data given by Goethals the unsaturated component appears to be *trans*. Goering, Cristol, and Dittmer (*J. Amer. Chem. Soc.*, **1948**, **70**, 3314) have described the preparation of a pent-3-enol of unspecified configuration by the lithium aluminium hydride reduction of methyl pent-2-enoate. Unfortunately these workers failed to characterise their product by crystalline derivatives, but from the method of preparation of the pent-2-enoic acid (hydrolysis of but-2-enyl cyanide, derived from crotyl chloride) we consider that it is largely or entirely *trans*. Finally Normant (*Compt. rend.*, **1948**, **226**, 733), by ring fission of 3-chloro-2-methyltetrahydrofuran with sodium, prepared a pent-3-enol which was not homogeneous. We had independently explored this route and shown that the product is a mixture of *cis*- and *trans*-pent-3-enol, and the evidence for this will be reported shortly. The mixed pent-3-enols were brominated in ether, and the dibromide dehydrobrominated by sodamide in liquid ammonia to give pent-3-ynol. From this, authentic pure *cis*- and *trans*-pent-3-enol have been prepared. *trans*-Pent-3-enol was made by reduction with sodium in liquid ammonia (cf. Sondheimer, *loc. cit.*), while the *cis*-isomer was obtained when the pentynol was hydrogenated over a palladium–calcium carbonate catalyst at room temperature. The two pent-3-enols had closely similar physical constants (see the table), but the 1-*naphthylurethane* of the *trans*-alcohol was a little higher-melting than the *cis*-derivative. The possibility that the *cis*-pent-3-enol contained a minor proportion of *trans*-isomer was considered, since it has been reported that semi-hydrogenation over Raney nickel or a supported nickel catalyst did not cause 100% *cis*-reduction (Henne and Greenlee, *J. Amer. Chem. Soc.*, **1943**, **65**, 2020). However, the proportion must be quite small, for the *cis*-hex-3-enoic acid derived from it was pure and we have found that the *trans*-acid is readily detected in derivatives of the *cis*-acid.

EXPERIMENTAL.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. The infra-red absorption spectra were determined with a Grubb Parsons spectrometer using the pure liquids in a cell of 30—50 μ. thickness.

cis-*Hex-3-enol* (*"Leaf Alcohol"*).—The "leaf alcohol" used and a sample of its 3 : 5-dinitrobenzoate were generously presented to us by Dr. M. Stoll and had been isolated from Japanese peppermint oil. On redistillation the main portion of the alcohol had b. p. 65—67°/19 mm., n_D^{20} 1·4384. We prepared the 1-naphthylurethane, m. p. 69—70°, which crystallised as colourless needles from light petroleum (b. p. 60—80°), in which it was rather more soluble than the *trans*-derivative. In a search for derivatives differing in m. p. from those of *trans*-hex-3-enol we prepared also the p-*nitrophenylurethane* as colourless crystals of uncertain shape [from light petroleum (b. p. 40—60°)], m. p. 72·5—73·5° (Found : C, 59·0; H, 6·1; N, 11·1. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%), and the p-*diphenylylurethane* as colourless prisms [from light petroleum (b. p. 80—100°)], m. p. 91·0—91·5° (Found : C, 77·2; H, 7·25. $C_{19}H_{21}O_2N$ requires C, 77·25; H, 7·2%).

The sample of the high-boiling fraction of Brazilian *Mentha Arvensis* oil, kindly supplied by Messrs. W. J. Bush & Co., had b. p. above 200° and a portion (220 g.) was therefore roughly fractionated in vacuum to give : (i) b. p. up to 100°/20 mm. (11 g.), (ii) b. p. 100—120°/18 mm. (85 g.), (iii) b. p. 135—150°/18 mm. (54 g.), and (iv) b. p. 150—165°/18 mm. (52 g.). Fractions (iii) and (iv) gave saponification equivalents corresponding to 31 and 45% of ester respectively, calculated as hexenyl phenylacetate. Fraction (iv) was hydrolysed by adding it in portions to a warm solution of potassium hydroxide (20 g.) in water (75 ml.) and completing the hydrolysis by heating the mixture on the steam-bath for 2 hours. Next day the hydrolysate was steam-distilled and the first 400 ml. of distillate were extracted with ether. The extract was dried (K_2CO_3) and distilled through a short column to give "leaf alcohol" (6·2 g.), b. p. 154—157°, n_D^{20} 1·4383. The 1-naphthylurethane, m. p. 71·0—71·5°, was slightly purer than that prepared from Dr. Stoll's hexenol, crystallising more readily in superior form, but gave no m. p. depression on admixture. Continued steam-distillation yielded a yellow oil, b. p. above 200°, evidently a neutral constituent of the original oil. The alkaline solution was then acidified and again steam-distilled, to yield an oily acid which did not crystallise when seeded with phenylacetic acid. It has not been further examined.

trans-*Hex-3-enol*.—*trans*-Hex-2-enoic acid was prepared by the method of Linstead, Noble, and Boorman (*loc. cit.*) and purified by partial freezing and rejection of the liquid layer. An ethereal solution of the acid (2·80 g.) was added slowly to lithium aluminium hydride (0·95 g.) dissolved in anhydrous ether (50 ml.). The reaction was completed by refluxing for one hour, cooling, and addition of water to destroy the excess of lithium aluminium hydride. The ethereal layer was washed with dilute acid and alkali, and on distillation gave trans-*hex-3-enol* (1·61 g.), b. p. 51—53°/9 mm., n_D^{20} 1·4374 (Found : C, 72·0; H, 12·2. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The 1-*naphthylurethane* formed needles (from light petroleum), m. p. 69—70° (Found : C, 75·8; H, 7·2; N, 5·6. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%), and when admixed with the 1-naphthylurethane of *cis*-hex-3-enol (1 : 1) melted at once when placed in a bath at 58°. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) in a freezing mixture and after one crystallisation had m. p. 43—46°; four recrystallisations raised this to m. p. 47—48° (Found : C, 53·6; H, 4·95; N, 9·5. $C_{13}H_{14}O_6N_2$ requires C, 53·05; H, 4·8; N, 9·5%). The p-*nitrophenylurethane* had m. p. 84—85° (Found : C, 59·0; H, 6·15; N, 11·0%), and the p-*diphenylylurethane* had m. p. 99·5° (Found : C, 77·3; H, 7·15%) [these derivatives were prepared from *trans*-hex-3-enol made by a new method (to be published) which gave a 1-naphthylurethane and 3 : 5-dinitrobenzoate identical with those described above]. The anthraquinone-2-carboxylate, in our hands, proved an unsatisfactory derivative; it was formed in low yield, was difficult to obtain crystalline, was photosensitive, and often showed a double m. p. (49—50° and 68—70°).

Hexenol from the Bouveault–Blanc Reduction of Ethyl Sorbate.—We are indebted to Prof. L. Ruzicka for the gift of a small specimen of the 1-naphthylurethane of this hexenol (cf. Ruzicka, Schinz, and Susz, *loc. cit.*). It sintered at 59—60°, melted to a turbid yellow melt at 61—63·5°, which became clear at 64·5°.

Pent-3-ynol.—The *cis-trans*-mixture of pent-3-enols (74 g.), prepared by the ring fission of 3-chloro-2-methyltetrahydrofuran, was diluted with ether (75 ml.), and bromine (141 g.) added dropwise, the temperature being kept below 25°. The ether was then sucked off by a water pump. If the temperature is allowed to rise much above 25° there is a tendency for hydrogen bromide to be eliminated with the formation of 3-bromo-2-methyltetrahydrofuran. Meanwhile sodamide was prepared by dissolving sodium (70 g.) in liquid ammonia (1·5 l.) in the presence of an iron catalyst (Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120). The 3 : 4-dibromopentanol was then added rapidly to the stirred solution of sodamide in liquid ammonia and stirred for 4 hours. A layer of ether was then added and the ammonia allowed to evaporate overnight. Next morning ammonia solution (*d* 0·880) and then water were added; the aqueous layer was thoroughly extracted with ether, and the bulked extracts were washed and dried. Fractional distillation gave pent-3-ynol (24·3 g.), b. p. 154—157°, n_D^{20} 1·4554 (Found: C, 69·5; 69·4; H, 9·95, 9·7. Calc. for C_5H_8O: C, 71·4; H, 9·6%). The 1-*naphthylurethane* formed needles [from light petroleum (b. p. 60—80°)], m. p. 119° (Found : C, 76·0; H, 6·1. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0%). A considerable quantity of a bromopentenol (3- or 4-bromopent-3-enol), containing vinyl bromide, was recovered from the higher-boiling fractions, b. p. 99°/14 mm., n_D^{20} 1·4897.

cis-*Pent-3-enol.*—Pent-3-ynol (52·5 g.) was hydrogenated at room temperature and atmospheric pressure in the presence of a palladium–calcium carbonate catalyst (1·5 g.; 10% of Pd) without use of a solvent. When 13·5 l. had been absorbed (Calc. for reduction to pentenol : 14·0 l.), filter cel was added, and the catalyst removed by filtration and washed with a little ether. Careful distillation of the filtrate gave cis-*pent-3-enol* (39·8 g.), b. p. 139—142°, n_D^{20} 1·4387 (Found : C, 69·4; H, 11·8. $C_5H_{10}O$ requires C, 69·7; H, 11·7%). The 1-*naphthylurethane* formed needles [from light petroleum (b. p. 60—80°)], m. p. 88—89° (Found : C, 75·2; H, 6·4. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·4%).

trans-*Pent-3-enol.*—Sodium (10 g.) was added to liquid ammonia (300 ml.) and then pent-3-ynol (5·0 g.) was added to the blue solution with stirring during 15 minutes. After stirring for a further 90 minutes ammonia solution (*d* 0·880) was added cautiously and the product set aside overnight to allow as much as possible of the ammonia to evaporate. Thorough extraction of the residue with ether, followed by washing, drying, and distillation, gave *trans*-pent-3-enol (3·0 g.), b. p. 136—137°, n_D^{20} 1·4340 (Found : C, 69·45; H, 11·6%). The 1-*naphthylurethane* formed needles, m. p. 93° (Found : C, 75·55; H, 6·55; N, 5·6%). A 1 : 1 mixture with the *cis*-1-naphthylurethane melted at 75—80°.

We gratefully acknowledge grants from the Agricultural Research Council, the Central Research Fund of the University of London, the Royal Society, and the Chemical Society which have defrayed the expenses of this investigation. We are also indebted to Prof. L. Ruzicka, Dr. M. Stoll, and Messrs. W. J. Bush and Co. for gifts of materials.

King's College (University of London), Strand, W.C.2. [*Received, November 19th, 1949.*]

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178. *Studies of Compounds related to Natural Perfumes. Part I. Concerning* cis- *and* trans-*Hex-3-en-1-ol.*

By Franz Sondheimer.

A convenient synthesis of hex-3-yn-1-ol (V) has been devised. Partial hydrogenation in the presence of palladium–calcium carbonate at room temperature gives an isomeric mixture of hex-3-en-1-ols, consisting mainly of the *cis*-isomer ("leaf alcohol"). Partial reduction of (V) with sodium in liquid ammonia gives exclusively *trans*-hex-3-en-1-ol (VIII), identical with that prepared by Crombie and Harper (preceding paper) and different from what had previously been considered the *trans*-isomer.

The acetylenic alcohol (V) is converted into the bromide (VI), which on attempted condensation with sodium acetylide in liquid ammonia undergoes dehydrobromination to hex-1-en-3-yne (VII). Similarly the ethylenic bromide (IX) with sodium acetylide gives hexa-1 : 3-diene (X).

In connexion with synthetical studies designed to elucidate the exact stereochemical configuration of the important violet-leaf constituents nona-2 : 6-dienol (I) and nona-2 : 6-

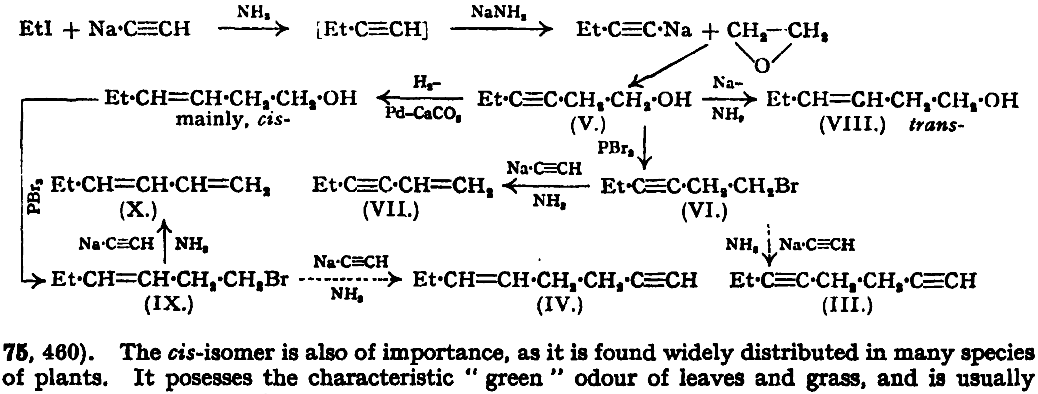
(I.) CHEt=CH·CH$_2$·CH$_2$·CH=CH·CH$_2$·OH CHEt=CH·CH$_2$·CH$_2$·CH=CH·CHO (II.)

dienal (II) (Ruzicka, Schinz, *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1602; 1944, **27**, 1561; Takei *et al.*, *Bull. Agric. Chem. Soc. Japan*, 1938, **14**, 64; *Chem. Zentr.*, 1938, II, 3696; Hunsdiecker, *Chem. Ber.*, 1947, **80**, 137), octa-1 : 5-diyne (III) and oct-5-en-1-yne (IV) were required. It was hoped to prepare these hydrocarbons from hex-3-yn-1-ol (V) and hex-3-en-1-ol by the action of sodium acetylide in liquid ammonia on the respective bromides (VI) and (IX). In fact it was found that these bromides were very readily dehydrobrominated to the hydrocarbons (VII) and (X) respectively (cf. Vaughn, Hennion, Vogt, and Nieuwland, *J. Org. Chem.*, 1937, **2**, 13), and the required hydrocarbons (III) and (IV) could not be obtained by this route. The diacetylene (III) was subsequently synthesised by a different method, and was successfully converted into nona-2 : 6-dienol (I) and the corresponding aldehyde (II) (Sondheimer, forthcoming publication). However, some interesting results were obtained in the present study concerning the *cis*- and *trans*-isomers of hex-3-en-1-ol and, as there exists some confusion about these compounds in the literature, it seemed desirable to record the results.

Hex-3-yn-1-ol (V) had previously been obtained from but-1-ynylmagnesium bromide and ethylene oxide (Stoll and Rouvé, *Helv. Chim. Acta*, 1938, **21**, 1542; Takei, Ono, and Sinosaki, *Ber.*, 1940, **73**, 950), the overall yield from the starting material, methyl ethyl ketone, being only *ca.* 1—6%. It may also be obtained by the dehydrobromination of the dibromide of hex-3-en-1-ol (Takei, Ono, and Sinosaki, *loc. cit.*; Bohnsack, *Ber.*, 1941, **74**, 1575; Stoll and Commarmont, *Helv. Chim. Acta*, 1949, **32**, 597). When ethyl iodide was treated in liquid ammonia with sodium acetylide (prepared directly from sodium and acetylene; cf. Raphael and Sondheimer, *J.*, 1950, 115), the highly volatile but-1-yne so formed was not isolated but was converted into the sodio-derivative by the addition of one mole of sodamide. Reaction with ethylene oxide then gave the required hex-3-yn-1-ol (V) (3 : 5-dinitrobenzoate; *α-naphthylurethane*) in 47% yield. After this work had been completed, the reaction between ethylene oxide and the sodio-derivative of 1-butyne (prepared separately) in liquid ammonia solution was reported by Newman and Wotiz (*J. Amer. Chem. Soc.*, 1949, **71**, 1292), who obtained hex-3-yn-1-ol in 48% yield.

The acetylenic carbinol was converted into the *bromide* (VI) by phosphorus tribromide, using various amounts of pyridine, but only in poor yield (cf. Tchao, *Bull. Soc. chim.*, 1933, **53**, 1533; Newman and Wotiz, *loc. cit.*, for the successful bromination of α-acetylenic primary alcohols). The same difficulty in the direct bromination of the β-acetylenic alcohol but-3-yn-1-ol was encountered by Jones and Whiting (private communication), who were however successful in brominating the corresponding toluene-*p*-sulphonate. The acetylenic bromide (VI) was treated with an excess of sodium acetylide in liquid ammonia, whereupon it underwent mainly dehydrobromination; no appreciable amount of the required diacetylene (III) was formed, and hex-1-en-3-yne (VII) could be isolated.

Attention was then turned to the partial reduction of hex-3-yn-1-ol (V). The hex-3-en-1-ol which could thereby be formed is of interest as the starting material for the synthesis of nona-2 : 6-dienol (I) and the corresponding aldehyde (II) (for references see above), and also of the important perfume jasmone (Treff and Werner, *Ber.*, 1935, **68**, 640; Hunsdiecker, *Ber.*, 1942, **75**, 460). The *cis*-isomer is also of importance, as it is found widely distributed in many species of plants. It posesses the characteristic " green " odour of leaves and grass, and is usually termed "leaf alcohol."* Partial hydrogenation of acetylenes in the presence of a colloidal palladium or Raney nickel catalyst is known to give the *cis*-ethylenic compounds (*inter al.*,



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* There exists some controversy in the literature regarding the stereochemical configuration of the natural hex-3-enol (Stoll and Rouvé, *loc. cit.*; *Ber.*, 1940, **73**, 1358; Takei, Ono, and Sinosaki, *loc. cit.*; Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; Crombie and Harper, *loc. cit.*), but previous evidence together with that presented in this paper clearly points to the *cis*-configuration.

Bourguel, *Bull. Soc. chim.*, 1929, **45**, [iv], 1067; Campbell and Eby, *J. Amer. Chem. Soc.*, 1941, **63**, 216, 2683; Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 148), and the catalytic semi-hydrogenation of hex-3-yn-1-ol has already been investigated by Stoll and Rouvé and by Takei, Ono, and Sinosaki (*locc. cit.*). The Swiss workers, using colloidal palladium, obtained a hex-3-enol, which was assigned the *cis*-configuration and shown to be identical with the natural hexenol ("leaf alcohol") as the 3 : 5-dinitrobenzoate after "five laborious crystallisations" had m. p. 44·5—46°, undepressed on admixture with the natural derivative (m. p. 48—48·5°). The Japanese workers using a palladium–barium sulphate catalyst found that the properties of the hydrogenation product were dependent on the temperature of hydrogenation, the pure natural hex-3-enol being formed at −18°.

On hydrogenation of hex-3-ynol (V) at room temperature in the presence of palladium–calcium carbonate, the uptake of hydrogen practically stopped after 1 mole of gas had been absorbed. The hex-3-enol so obtained was very similar to that reported by Stoll and Rouvé, both in its physical properties and in the fact that the 3 : 5-dinitrobenzoate required seven crystallisations to achieve constant melting point (48—48·5°; undepressed on admixture with the derivative of natural hexenol, m. p. 49—50°). The α-naphthylurethane also needed three crystallisations to reach constant melting point (69—69·5°; undepressed on admixture with the natural derivative, m. p. 70—70·5°). It thus seemed that, although the hex-3-en-1-ol obtained by catalytic hydrogenation consisted predominantly of the *cis*-isomer, it contained an impurity, possibly the *trans*-isomer. This has been confirmed by its infra-red spectrum described below.

A hex-3-en-1-ol has been prepared by the Bouveault–Blanc reduction of ethyl sorbate (Ruzicka and Schinz, *Helv. Chim. Acta*, 1934, **17**, 1602; Takei, Imaki, and Tada, *Ber.*, 1935, **68**, 953), differing from the natural material by its sharper smell and the lower melting points of its derivatives (3 : 5-dinitrobenzoate, m. p. 28°; α-naphthylurethane, m. p. 61—63°). It was considered to be stereoisomeric with the natural (*cis*-)hexenol, *i.e.*, to have the *trans*-configuration (Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; cf. Takei, Imaki, and Tada, *loc. cit.*). Partial reduction of acetylenic hydrocarbons and tertiary carbinols by means of sodium in liquid ammonia has been shown to give the *trans*-ethylenic compounds (Campbell and Eby, and Campbell and Campbell, *locc. cit.*). When the primary alcohol hex-3-yn-1-ol (V) was treated in this way, the trans-*hex*-3-*en*-1-*ol* (VIII) so formed in good yield was found to be different from that obtained by the Bouveault–Blanc reduction of ethyl sorbate. Its derivatives (3 : 5-*dinitrobenzoate*, m. p. 46—46·5°; *α-naphthylurethane*, m. p. 68—69°) were considerably higher-melting than those of the Bouveault–Blanc product and, although the melting points of the *trans*-hexenol derivatives were nearly identical with those of the *cis*-isomer, considerable depressions were observed on admixture.

Independently of this work, Crombie and Harper (*loc. cit.*) found that both by the action of lithium aluminium hydride on *trans*-pent-2-ene-1-carboxylic acid, and also by the ring fission of the α-form of 3-chloro-2-ethyltetrahydrofuran, a *trans*-hex-3-enol was obtained, also differing from that described by Ruzicka and Schinz. The melting points of the derivatives of the *trans*-hexenol reported by Crombie and Harper are identical with those of the *trans*-hexenol (VIII) described in the present communication, and identity was established by mixed-melting-point determinations. It is highly probable that the so-called *trans*-isomer of Ruzicka and Schinz was not homogeneous. Nevertheless it must have contained a considerable percentage of the *trans*-hexenol, as the nona-2(*trans*) : 6(*trans*)-dienal prepared from it was shown to be identical with a sample prepared by an independent method (Hunsdiecker, *Chem. Ber.*, 1947, **80**, 137).

The infra-red spectra of the *cis*- and *trans*-hex-3-enols have already been recorded and discussed by Crombie and Harper (*loc. cit.*). The spectrum of the *trans*-isomer (VIII) obtained by the sodium–liquid ammonia reduction of hexynol (Fig. 1) is closely similar to that previously recorded, showing the typical strong "*trans*"-absorption band at 10·3 μ. (Rasmussen, Brattain, and Zucco, *J. Chem. Physics*, 1947, **15**, 135). The infra-red spectrum of the natural (*cis*-)hex-3-enol has been given by Crombie and Harper (*loc. cit.*), while Fig. 2 shows the spectrum of the hex-3-enol obtained by the catalytic hydrogenation of hexynol. The bands at 11·5 and 13·8 μ. in Fig. 2 are typical for the *cis*-isomer, not being shown by the *trans*-form. On the other hand, the "*trans*"-band at 10·3 μ. is also quite marked. From these data, combined with the fact that on repeated crystallisation the *cis*-derivatives are obtained, it is concluded that catalytic hydrogenation of hexynol (V) under the conditions employed gives a *cis-trans*-mixture of hex-3-en-1-ols, consisting predominantly of the *cis*-isomer.

The hex-3-enol (mainly *cis*-) was converted into the bromide (IX), and this was treated with sodium acetylide in liquid ammonia. Again no appreciable amount of the hydrocarbon (IV) could be isolated, dehydrobromination to hexa-1 : 3-diene (X) (determined quantitatively by its ultra-violet light absorption maximum at 2280 A.) being the principal reaction.

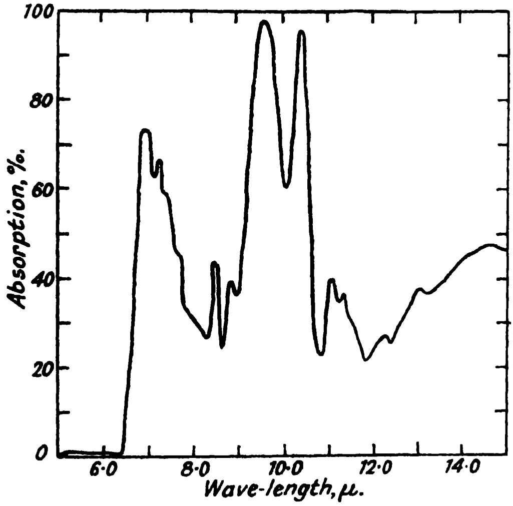

FIG. 1.
trans-*Hex-3-enol from* Na *reduction.*

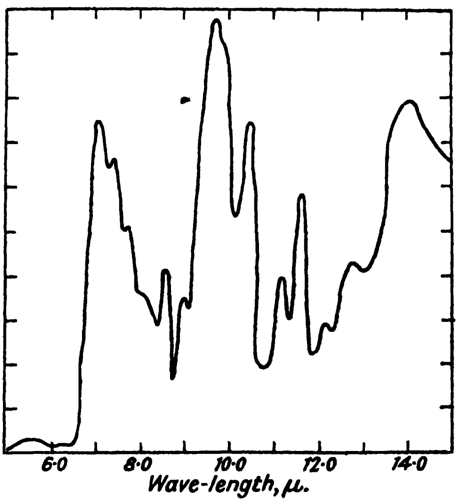

FIG. 2.
Hex-3-enol from catalytic hydrogenation.

EXPERIMENTAL.

Hex-3-yn-1-ol (V).—Sodium (40 g., 1·74 g.-mols.) was added in small pieces to liquid ammonia (1·5 l.) through which acetylene was bubbled, with stirring and cooling (alcohol–carbon dioxde). The acetylene flow was stopped at the exact moment when the blue colour disappeared after the last piece of sodium had been added (to ensure that no excess of acetylene was present in solution), and ethyl iodide (250 g., 1·6 g.-mols.) in dry ether (250 c.c.) was introduced during the course of 45 minutes. The cooled reaction mixture was stirred for 4 hours and the 1-butyne so formed was converted into the sodio-complex by addition, in several portions, of a cooled sodamide suspension in liquid ammonia (1 l.), made from sodium (40 g.), the ferric nitrate catalyst of Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used. After another hour's stirring, ethylene oxide (141 g., 3·2 g.-mols.) was added all at once, and the reaction mixture was stirred for 24 hours, the temperature being held at *ca.* −40°. Ammonium chloride (120 g.) was gradually introduced, and the ammonia evaporated on the steam-bath. Water and ether were added to the residue, and the aqueous layer washed twice with ether. The combined ethereal extracts, after being washed with a small volume of water, were dried ($MgSO_4$) and evaporated. A preliminary distillation, followed by fractionation through a Dufton column, then gave hex-3-yn-1-ol (73·2 g., 47% calc. on ethyl iodide), b. p. 163—164°/772 mm., 73·5—74·5°/23 mm., n_D^{17} 1·4579 (Stoll and Rouvé, *Helv. Chim. Acta*, 1938, **21**, 1542, give b. p. 65·5—66°/12 mm., n_D^{20} 1·4530). The 3 : 5-dinitrobenzoate after one crystallisation from light petroleum (b. p. 60—80°) had constant m. p. 73—74° (Found : C, 53·6; H, 4·1; N, 9·65. Calc. for $C_{13}H_{12}O_6N_2$: C, 53·4; H, 4·1; N, 9·6%) (Newman and Wotiz, *loc. cit.*, give m. p. 72—73°; Stoll and Commarmont, *loc. cit.*, give m. p. 75—76° and 80—81°). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in small needles, m. p. 84—85° (Found : C, 76·45; H, 6·4; N, 5·35. $C_{17}H_{17}O_2N$ requires C, 76·35; H, 6·4; N, 5·25%). In addition a higher-boiling product (13 g.) was obtained, b. p. 116—120°/23 mm., n_D^{17} 1·4628, which was not further investigated.

1-*Bromohex-3-yne* (VI).—Phosphorus tribromide (27 g.) in dry ether (15 c.c.) was slowly added to a cooled and stirred solution of hex-3-yn-1-ol (16 g.) in ether (65 c.c.), the temperature being kept at −5°. After being stirred at −5° for a further 90 minutes, the reaction mixture was poured on ice and water. The organic layer was washed with sodium hydrogen carbonate solution and water, and dried. Removal of ether, followed by distillation of the residue, gave 1-*bromohex-3-yne* (3·75 g., 14%) as a colourless liquid, b. p. 63·5—65·5°/18 mm., $n_D^{17.5}$ 1·4890 (Found : Br, 49·1. C_6H_9Br requires Br, 49·6%).

In another experiment, the general conditions of Tchao (*loc. cit.*) were employed. Phosphorus tribromide (14·5 g.) was added dropwise to a cooled mixture of pyridine (0·6 g.) and hex-3-ynol (12·6 g.), with constant stirring during 30 minutes. The reaction mixture was then heated under reflux on the steam-bath for 3 hours, and the product isolated as before. This yielded the bromide (2·4 g., 12%), b. p. 67—68°/25 mm., n_D^{17} 1·4931. In addition, a higher-boiling liquid was obtained, b. p. 99—100°/25 mm., n_D^{17} 1·5222, giving analytical figures correct for the hydrogen bromide adduct of 1-bromohex-3-yne (Found : Br, 65·55. $C_6H_{10}Br_2$ requires Br, 66·05%).

The conditions of Juvala (*Ber.*, 1930, **63**, 1990) were also employed, using hex-3-ynol (16 g.), pyridine (2·8 g.), and phosphorus tribromide (17·4 g.). This gave a mixed product which could only have contained a very small proportion of the required bromide. Hex-3-en-1-ol can be successfully converted into the bromide under these conditions (see below).

Hex-1-*en*-3-*yne* (VII).—A suspension of sodium acetylide in liquid ammonia (100 c.c.) was prepared by adding sodium (1·2 g.) to the stirred and cooled (alcohol–carbon dioxide) liquid, through which acetylene was being passed. As soon as the colour was discharged, the acetylene flow was reduced, and the acetylenic bromide (3·2 g.) in dry ether (3 c.c.) was added. The cooled reaction mixture was stirred for a further 5 hours, ammonium chloride (4 g.) added, and the solvent removed on the steam-bath. Water and ether were added to the residue, the ethereal layer was washed with sodium hydrogen carbonate solution and water, and dried. The solvent was removed through a short Vigreux column, and the residue distilled. This yielded hex-1-en-3-yne (0·5 g.) as a colourless liquid, b. p. 83—85°/762 mm., n_D^{18} 1·449 (Found: C, 90·45; H, 10·1. Calc. for C_6H_8: C, 89·95; H, 10·05%) (Jacobson and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 1622, give b. p. 84·5—85·3°/758 mm., n_D^{20} 1·4522). The distillation residue (0·3 g.) consisted of a viscous brown gum.

Catalytic Partial Hydrogenation of Hex-3-*yn*-1-*ol* (V).—The acetylenic carbinol (14·7 g.) in methyl acetate (30 c.c.) was shaken with Raney nickel for 1 hour to remove the small amount of catalyst poison present. The metal was filtered off and well washed with methyl acetate. The filtrate was shaken in hydrogen in the presence of palladium–calcium carbonate (1·5 g.; 5% of Pd). About 3 l. of gas were rapidly absorbed during 1 hour, whereafter the uptake slowed down. After the absorption of 3590 c.c. of gas (15°/758 mm.; 0·99 mole) the uptake had practically stopped. The catalyst was filtered off, the solvent removed, and the residue distilled. This yielded impure *cis*-hex-3-en-1-ol (13·1 g.), b. p. 156—157°/765 mm., 74—75°/29 mm., n_D^{17} 1·4430, having an odour very similar to that of a sample of natural (*cis*-)hexenol [Stoll and Rouvé, *loc. cit.*, give b. p. 59—61°/12·5 mm., n_D^{24} 1·4373, for the hexenol obtained by catalytic hydrogenation; Ruzicka, Schinz, and Susz, *loc. cit.*, give b. p. 58—58·5°/12 mm., n_D^{20} 1·4380, for pure natural (*cis*-)hexenol regenerated from the crystalline allophanate].

Derivatives of cis-*Hex*-3-*en*-1-*ol*.—The above isomeric mixture was converted into the 3 : 5-dinitrobenzoate in the usual manner. After one crystallisation from light petroleum (b. p. 40—60°) it formed long needles, m. p. 34—35°. After another six crystallisation from this solvent or pentane, the 3 : 5-dinitrobenzoate of *cis*-hexenol was obtained, having constant m. p. 48—48·5° (Found: C, 53·1; H, 4·85; N, 9·65. Calc. for $C_{13}H_{14}O_6N_2$: C, 53·05; H, 4·8; N, 9·5%); this m. p. was not depressed on admixture with a sample (m. p. 49—50°) obtained from the natural hexenol.

The α-naphthylurethane prepared from the isomeric mixture had, after two crystallisations from light petroleum (b. p. 40—60°), m. p. 68°, and after another crystallisation the pure α-naphthylurethane of *cis*-hexenol was obtained as long needles, having constant m. p. 69—69·5° (Found: C, 75·95; H, 7·2; N, 4·9. Calc. for $C_{17}H_{19}O_2N$: C, 75·8; H, 7·1; N, 5·2%); this m. p. was not depressed on admixture with a specimen (m. p. 70—70·5°) obtained from the natural alcohol.

trans-*Hex*-3-*en*-1-*ol* (VIII).—Hex-3-yn-1-ol (4·9 g.), dissolved in dry ether (5 c.c.), was gradually added to a stirred and cooled (alcohol–carbon dioxide) solution of sodium (4·6 g.) in liquid ammonia (200 c.c.). Stirring was continued for a further 2 hours, whereafter the blue reaction mixture was decomposed with ammonium chloride (15 g.). The ammonia was evaporated off on the steam-bath, water and ether were added to the residue, the aqueous layer was once more extracted with ether, and the combined organic extracts were washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried solution was evaporated. Distillation of the residue then gave trans-*hex*-3-*en*-1-*ol* (3·7 g., 75%) as a colourless mobile liquid, b. p. 152—153·5°/762 mm., n_D^{18} 1·4406, possessing a characteristic odour distinctly different from the " green " odour of the *cis*-isomer (Found: C, 72·0; H, 12·15. $C_6H_{12}O$ requires C, 71·95; H, 12·1%) (Ruzicka, Schinz and Susz, *loc. cit.*, give b. p. 58·5—60°/12 mm., n_D^{20} 1·4376, for the " *trans* "-isomer obtained by the Bouveault–Blanc reduction of ethyl sorbate).

The 3 : 5-*dinitrobenzoate* was formed in quantitative yield, having m. p. 45—46°; after one crystallisation from light petroleum (b. p. 40—60°) it formed needles having constant m. p. 46—46·5° (Found: C, 53·1; H, 4·9; N, 9·55. $C_{13}H_{14}O_6N_2$ requires C, 53·05; H, 4·8; N, 9·5%). This m. p. was not depressed on admixture with a sample (m. p. 47°) derived from the lithium aluminium hydride reduction of *trans*-pent-2-ene-1-carboxylic acid (Crombie and Harper, *loc. cit.*). On admixture with the *cis*-derivative (m. p. 48—48·5°) described above, the m. p. was 33—35°.

The α-*naphthylurethane* after one crystallisation from light petroleum (b. p. 40—60°) formed needles, m. p. 68—69°, not raised by further crystallisation (Found: C, 75·55; H, 7·1; N, 5·35. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%). The m. p. was not depressed on admixture with a sample (m. p. 68·5—69·5°) prepared by Crombie and Harper (*loc. cit.*). On admixture with the " *trans* "-derivative (m. p. 61—63°), prepared from ethyl sorbate (Ruzicka, Schinz, and Susz, *loc. cit.*), the m. p. was 51—53°. On admixture with the *cis*-derivative (m. p. 69—69·5°) described above, the m. p. was 56—60°.

Hexa-1 : 3-*diene* (X).—The hex-3-enol (mainly *cis*-) obtained from the catalytic hydrogenation of the acetylene was converted into the bromide (IX) by the general method of Juvala (*loc. cit.*), as has already been described for the natural (*cis*-)hexenol (Treff and Werner, *loc. cit.*; Hunsdiecker, *Ber.*, 1942, **75**, 460). The 1-bromohex-3-ene so obtained in *ca.* 50% yield had b. p. 49—51°/20 mm., n_D^{20} 1·473.

The ethylenic bromide (3·2 g.) was treated with sodium acetylide (from 1·2 g. of sodium) in liquid ammonia (100 c.c.) as described above for the acetylenic bromide. The reaction was allowed to proceed for 3·5 hours, and the mixture was then carefully poured on ice and *n*-hexane (without evaporating the ammonia, so as not to lose any of the volatile product). The organic layer was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The solvent, containing the hexa-1 : 3-diene (Prévost, *Ann. Chim.*, 1928, **10**, 176; *Bull. Soc. chim.*, 1941, **8**, 89) was carefully distilled off through a Dufton column, until the distillation temperature reached 75°. The residue (0·25 g.) was dark and viscous, and could not be distilled. The hexane distllate (180 c.c.) had light absorption: Maximum, 2280 A.; $E^{1\%}_{1\,\text{cm.}} = 14·5$. This corresponds to a *ca.* 0·97-g. content of hexa-1 : 3-diene (60% yield), assuming $\varepsilon = 22,000$ for the pure diene.

The author thanks Sir Ian Heilbron, D.S.O., F.R.S., for his interest in this work, and Drs. S. H. Harper and L. Crombie for interesting discussions and samples used for mixed-m. p. determinations. He is also indebted to the Department of Scientific and Industrial Research for a

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Imperial College of Science and Technology, London, S.W.7.
Converse Memorial Laboratory, Harvard University,
Cambridge 38, Mass., U.S.A.

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179. *The Solubility Products of Ferrous and Ferrosic Hydroxides.*

By T. V. Arden.

Values of 2·4 × 10^{-14} and 6·4 × 10^{-18} for the solubility products of ferrous hydroxide and freshly precipitated green ferrosic hydroxide have been obtained by potentiometric titration with sodium hydroxide in sulphate solution, using a glass electrode.

The precipitation of ferrous hydroxide has been widely studied, and the solubility product determined by a variety of methods. The highest value recorded, 7 × 10^{-13}, was obtained by Schrager (*Coll. Czech. Chem. Comm.*, 1929, **1**, 275), while the lowest, 2·5 × 10^{-21}, was given by Bodlander (*Z. Elektrochem.*, 1900, **8**, 840). The latter value was confirmed by Britton (*J.*, 1925, **127**, 2110), by potentiometric titration of ferrous sulphate with sodium hydroxide, using a hydrogen electrode. The same method was used by Elder (*Trans. Amer. Electrochem. Soc.*, 1930, 57) who obtained a figure of 4·8 × 10^{-16}. Conductivity measurements of saturated ferrous hydroxide solutions were used by Lamb (*J. Amer. Chem. Soc.*, 1910, **32**, 1214), and by Murata (*J. Soc. Chem. Ind. Japan*, 1932, **35**, 523), to calculate values of 9·9 × 10^{-15} and 2·9 × 10^{-15} respectively. Shipley and McHaffie (*Canadian Chem. Met.*, 1924, **8**, 5, 121) determined the solubility product of ferrous hydroxide as 3·9 × 10^{-15}, from observations of the rate of corrosion of metallic iron in oxygen-free water. The solubilities of metallic iron in pure water, and in potassium hydroxide solution, were shown by Bineau (*Compt. rend.*, 1879, **41**, 509) and Krassa (*Z. Elektrochem.*, 1909, **15**, 491) to be 7·5 × 10^{-5} and 2·8 × 10^{-5} respectively, giving solubility products of 2·0 × 10^{-13} and 8·7 × 10^{-14}, assuming complete ionisation. Whitman, Russell, and Davis (*J. Amer. Chem. Soc.*, 1925, **47**, 70) showed that ferrous hydroxide is only 30% ionised in saturated solution, the undissociated molecules being in true solution. The solubility of metallic iron in pure water at 25° was found to be 6·7 × 10^{-5}, in agreement with the results of Bineau; but the solubility product, calculated from determinations of the pH of the saturated solution, was 3·2 × 10^{-14}. A recalculation of Bineau's and Krassa's results, with allowance for the degree of ionisation of ferrous hydroxide, gives values of 4·1 × 10^{-14} and 2·6 × 10^{-14}, respectively, for the solubility product.

The product of the reaction of pure ferrous sulphate solution with alkali is a white gelatinous precipitate, which becomes green in the presence of traces of ferric salts, owing to the presence of ferrosic hydroxide. The green compound is formed at a pH (6·4 in 0·05M-solution) considerably lower than that of pure ferrous hydroxide (8·1 in 0·05M-solution); and it is therefore necessary, in studying the precipitation of ferrous hydroxide, to eliminate both ferric iron and free oxygen from the system. It is extremely difficult to remove all traces of Fe^{+++}, and in a titrimetric procedure failure to prevent oxidation would result in low values for the solubility product. In the case of Britton's experiments, it was stated that air was not completely excluded. In methods based upon determinations of the solubility of iron in water (Bineau, Krassa, Lamb, Murata, and Whitman) the effect of traces of oxygen would be to raise the apparent solubility product; but the resulting errors would be small, since the solutions produced by this method are sufficiently alkaline to render the solubility of ferric iron negligible. The true solubility product of ferrous hydroxide therefore appears to be of the order of 10^{-14}, and results which are considerably lower than this figure are likely to have been influenced by oxidation.

The object of this work has been to determine $K_{Fe(OH)_2}$ from measurements of the changes in pH during a titration of ferrous sulphate with sodium hydroxide, in the complete absence of ferric iron or oxygen. In addition, the precipitation of ferrosic hydroxide has been studied, by titrations of mixtures of ferric and ferrous sulphates, in varying ratios. Titrations have also been carried out in the presence of atmospheric oxygen, to demonstrate the large errors which are caused in these conditions.

Experimental.

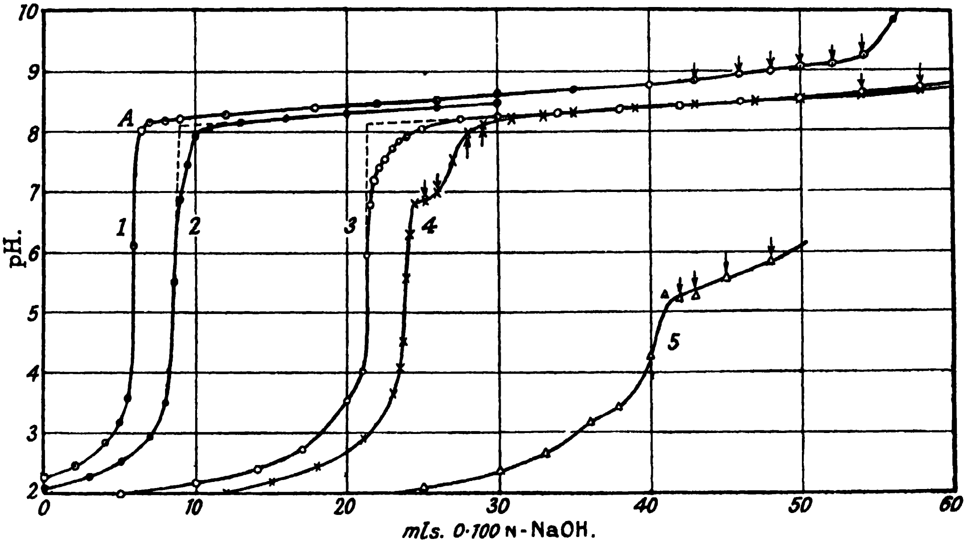
Ferrous Sulphate Solution.—A stock solution of 0·05M-ferrous sulphate, containing 0·05M-H_2SO_4, was prepared from pure metallic iron, and AnalaR sulphuric acid. It was impossible to maintain this solution in a fully reduced condition, and a further reduction was therefore carried out immediately before each titration, by boiling a measured portion of the solution with metallic iron or magnesium in the sealed titration vessel. The experiment was then carried out under an atmosphere of hydrogen, the passage of which also served to agitate the solution. When iron was used for the reduction, the total ferrous content of the solution was determined at the end of the experiment; when magnesium was used, no interference with the titration was caused, since the step in the titration curve caused by the precipitation of magnesium hydroxide occurred at pH 10·5, after the completion of the ferrous r ion.

ric Sulphate Solution.—A solution containing 0·033M-ferric sulphate and 0·05M-H_2SO_4 was prepared by dissolving metallic iron in sulphuric acid, and oxidising with AnalaR hydrogen peroxide. The excess of peroxide was removed by prolonged boiling, and the solution was de-aerated immediately before each use by the prolonged passage of hydrogen.

Sodium Hydroxide Solution.—A solution (0·100N.) of sodium hydroxide was de-aerated by the prolonged passage of hydrogen immediately before each experiment.

Ferrous Hydroxide Precipitation.—A portion of the stock ferrous solution, initially at pH 1·5, was reduced and titrated with sodium hydroxide at 20°, the pH being determined by means of a glass electrode and a dip-type calomel half-cell. The electrode system was standardised before and after each experiment at pH 3·97 and 9·18, no results being accepted unless the four standardisation readings agreed within pH 0·05. After each addition of alkali, the pH was allowed to reach equilibrium. In the early stages of the titration, this process took place rapidly, but during the final stages of precipitation the pH dropped slowly to the values shown. (The direction and magnitude of changes of pH with time are indicated by arrows touching the curves.) In the complete absence of ferric iron, sharp inflexions occurred at the point corresponding to the first permanent white precipitate (*A*, Fig. 1, Curve 1). In the presence of small traces of Fe^{+++}, the inflexions were less clearly defined (Fig. 1, Curves 2 and 3), and the formation of ferrous hydroxide was preceded by formation of traces of green ferrosic hydroxide. The true pH of first precipitation could nevertheless be determined by extrapolation of the horizontal and vertical portions of the curves. When sufficient ferric iron was present to give a definite green colour to the precipitate, the resultant curves were considerably distorted (Fig. 1, Curve 4) and were not used for the calculation of results. In a typical experiment, 50 ml. of 0·0500M-ferrous sulphate solution were reduced with magnesium, and titrated with 0·100N-sodium hydroxide. The point of first precipitation (*A*, Fig. 1, Curve 1) occurred after the addition of 6·1 ml. of alkali, when the total volume was 56·1 ml. The concentration of ferrous iron, $[Fe^{++}]$, is $0·05 \times 50/56·1 = 4·48 \times 10^{-2}$. The pH was then 8·10, and since K_w at 20° is $10^{-14·18}$, $[OH']$ is $10^{-6·08}$.

FIG. 1.



Then $K = [Fe^{++}] \times [OH']^2 = 4·48 \times 10^{-2} \times 10^{-12·16} = 3·1 \times 10^{-14}$, where K is the apparent solubility product, assuming complete dissociation of ferrous sulphate, and neglecting activity corrections.

The following results are calculated from curves in which the distortion is less than in curve 3 (Fig. 1)

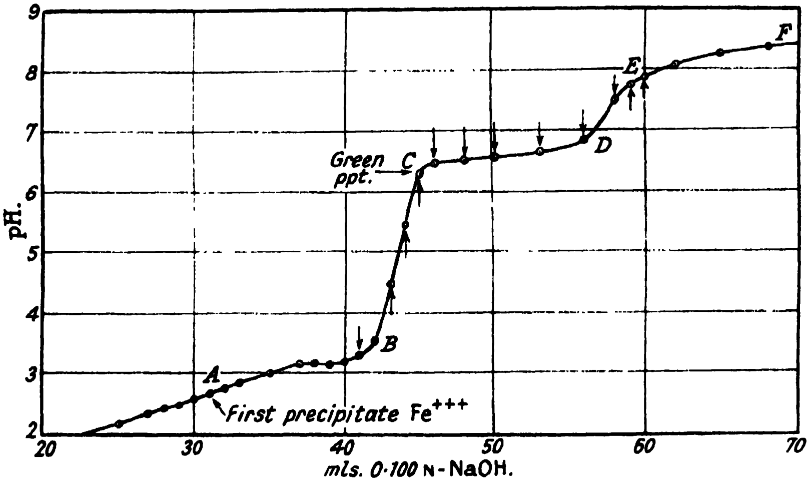
Expt.	$[Fe^{++}]$ at *A*.	pH.	$[OH']$.	Solubility product.
1	$4·48 \times 10^{-2}$	8·10	$10^{-6·08}$	$3·1 \times 10^{-14}$
2	$3·24 \times 10^{-2}$	8·15	$10^{-6·03}$	$2·8 \times 10^{-14}$
3	$4·23 \times 10^{-2}$	8·00	$10^{-6·18}$	$1·9 \times 10^{-14}$
4	$3·5 \times 10^{-2}$	8·10	$10^{-6·08}$	$2·4 \times 10^{-14}$
5	$8·10 \times 10^{-3}$	8·44	$10^{-5·74}$	$3·0 \times 10^{-14}$
6	$8·10 \times 10^{-3}$	8·40	$10^{-5·78}$	$2·2 \times 10^{-14}$
7	$3·96 \times 10^{-3}$	8·5	$10^{-5·7}$	$1·6 \times 10^{-14}$

The agreement between experiments at different concentrations is good, and gives a mean value $K = 2{\cdot}4 \times 10^{-14}$.

Titration in the Presence of Air.—A titration carried out in a closed vessel containing some air gave a precipitate, largely composed of ferric hydroxide, with some ferrosic hydroxide, at pH 5·25. The resultant curve (Curve 5, Fig. 1) resembles that obtained by Britton, and the apparent solubility product calculated from it is $5{\cdot}3 \times 10^{-20}$.

Ferrosic Hydroxide Precipitation.—The procedure described for ferrous hydroxide was used, with the addition of a measured quantity of 0·033M-ferric sulphate solution after reduction of the ferrous solution. In a typical experiment (Fig. 2), 15 ml. of 0·033M-Fe^{+++} and 50 ml. of 0·05M-Fe^{++} were titrated with 0·100M-NaOH. Basic ferric sulphate was first precipitated between pH 2·5 and 3·5, the curve (*A*—*B*) being of the characteristic type observed by Evans and Prior (*J.*, 1949, S 157). The complete precipitation of ferric iron was followed by further reaction of the precipitate with sodium hydroxide to form $Fe(OH)_3$, the pH rising rapidly during this process (*B*—*C*). At *C*, the formation of dark olive-green ferrosic hydroxide was accompanied by a sharp inflexion in the curve, and in the region *C*–*D*, the pH readings dropped slowly after each addition of alkali, to the values shown. If the normally accepted formula for ferrosic hydroxide is assumed, the reaction in the region *C*–*D* is

Fig. 2.



$$2Fe(OH)_3 + Fe^{++} + 2OH' = Fe_3(OH)_8$$

and the solubility product of $Fe_3(OH)_8$ is therefore $K' = [Fe^{++}] \times [OH']^2$. The end point of this reaction was marked by an inflexion at *D*, after which the pH readings rose rapidly on to a curve *E*—*F* similar to those obtained with pure ferrous iron solutions.

Results were as follows :

Expt.	$[Fe^{++}]$ at *C*.	pH.	[OH'].		*K*.
1	$2{\cdot}38 \times 10^{-2}$	6·35	$10^{-7{\cdot}83}$		$5{\cdot}2 \times 10^{-18}$
2	$3{\cdot}20 \times 10^{-2}$	6·40	$10^{-7{\cdot}78}$		$8{\cdot}9 \times 10^{-18}$
3	$2{\cdot}35 \times 10^{-2}$	6·35	$10^{-7{\cdot}83}$		$5{\cdot}1 \times 10^{-18}$
				Mean	$6{\cdot}4 \times 10^{-18}$

DISCUSSION.

Ferrous Hydroxide.—The value $2{\cdot}4 \times 10^{-14}$ for the solubility product is in good agreement with the results obtained by Bineau and by Whitman, from solubility determinations, and by Müller from the Fe^{+++}/Fe^{++} potential. The titration curves are variable in length, the molecular ratio of sodium hydroxide required to give complete precipitation being between 1·7 and 1·9. This is in agreement with the findings of Pickering (*J.*, 1907, 91, 1981), who considered the precipitate to be $10FeO,SO_3$. The formation of such a compound is normally accompanied, however, by a clear inflexion at the end of precipitation, as in the case of $4CuO,SO_3$, or $5ZnO,SO_3$. In the case of ferrous iron the final inflexions are ill-defined, and in the last stages of the curve, the pH readings fall slowly when the solution is kept. This effect could result from the occlusion of ferrous sulphate on a precipitate of ferrous hydroxide, and the formation of a basic ferrous sulphate cannot therefore be inferred from this work.

Ferrosic Hydroxide.—The term " ferrosic hydroxide " has been applied to compounds with widely differing properties, and the value $6{\cdot}4 \times 10^{-18}$ for the solubility product applies only to the compound produced from mixed ferric and ferrous solutions under conditions of rising pH.

The addition of excess of alkali causes the formation of a black compound, insoluble in mineral acids, which has not been studied in detail. The rate of fall of pH in the later stages of the curve *C–D* was so slow that equilibrium was not always attained, and the length *C–D* has been found variable. In all cases, however, the length of this curve was considerably greater than that required for $Fe_3(OH)_8$, and corresponds with the formation of $Fe_4(OH)_{10}$ [in Fig. 2, Found : 11 ml., $Fe_3(OH)_8$ requires 5·0 ml. $Fe_4(OH)_{10}$ requires 10·0 ml.]. A compound corresponding to this formula was prepared by Baudisch and Merzer (*Biochem. Z.*, 1920, **87**, 107) who considered it to be $HO{\cdot}Fe{\cdot}O{\cdot}Fe(OH)_2$. It appears that this compound is formed under the conditions of these experiments, by further reaction of $Fe_3(OH)_8$ in the presence of excess of ferrous iron.

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CHEMICAL RESEARCH LABORATORY, TEDDINGTON. [*Received, November 24th,* 1949.]

180. *Aminoalkyl Tertiary Carbinols and Derived Products. Part II. 3-Amino-1 : 1-di-2'-thienyl-alkan-1-ols and -alk-1-enes.*

By D. W. ADAMSON.

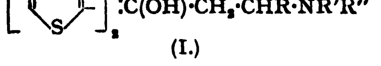
3-*Amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2'-*thienylalkan*-1-*ols* (I) were prepared from 2-thienyl-lithium and 2-aminoalkanecarboxylates (II), obtained by addition of the appropriate amine to substituted acrylic esters. Substantial quantities of 2-β-piperidinopropionylthiophen (III), as well as the carbinol, were isolated in the Grignard reaction between 2-thienylmagnesium bromide and ethyl β-piperidinopropionate. The amino-carbinols were dehydrated to the 3-*amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2'-*thienylalk*-1-*enes* (IV).

Several amino-carbinols had high antispasmodic activity and a number of *NN*-disubstituted 3-*amino*-1 : 1-*di*-2'-*thienylbut*-1-*enes* were potent analgesics.

A NUMBER of the *N*-substituted 3-amino-1 : 1-diphenyl-propan-1-ols and -prop-1-enes described in Part I (*J.*, 1949, S 144) had interesting pharmacological properties (White, Fawcett, Green, and Hudson, to be published). The investigation of related compounds in which both phenyl groups of the parent compound are replaced by 2-thienyl groups, the synthesis of which is now described, forms part of our programme in this series.

Several *NN*-disubstituted 3-*amino*-1 : 1-*di*-2'-*thienylpropan*-1-*ols* (I; R = H) were prepared by reaction of 2-thienyl-lithium with ethyl *NN*-disubstituted β-aminopropionates (II; R' = H). 3-*Amino*-1 : 1-*di*-2'-*thienylbutan*-1-*ol* (I; R = Me; R' = R'' = H) and an extensive series of *N*-substituted derivatives were obtained similarly from the appropriate β-aminobutyrates (II; R' = Me), and the method was extended to the preparation of 3-*dimethylamino*-1 : 1-*di*-2'-*thienyl*-*pentan*-1-*ol*, -*hexan*-1-*ol*, and -4-*methylpentan*-1-*ol* (I; R = Et, Pr^n, or Pr^i; R' = R'' = Me) from the corresponding *methyl 2-dimethylaminoalkanecarboxylates*. The yields of tertiary amino-carbinols were good, but those of the primary and secondary amino-butanols were less satisfactory (cf. Part I, *loc. cit.*) (Table II). The tertiary amino-carbinols were converted into water-soluble ***hydrochlorides*** or ***hydrogen oxalates*** and some into ***methiodides***; the primary and secondary amino-carbinols gave neutral ***oxalates***.

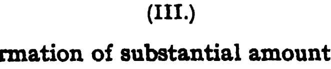
The yields of amino-carbinol were poor in the two examples in which the Grignard reaction was employed. Ethyl β-piperidinopropionate on reaction with 2-thienylmagnesium bromide (3 mols.) gave 2-β-piperidinopropionylthiophen (III) in 23% yield in addition to the expected 3-*piperidino*-1 : 1-*di*-2'-*thienylpropan*-1-*ol* (I; R = H; NR'R'' = $N{<}C_5H_{10}$) in similar yield.



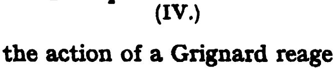
(I.)

$CO_2R{\cdot}CH_2{\cdot}CHR'{\cdot}NR''R'''$

(II.)



(III.)



(IV.)

The formation of substantial amounts of ketone by the action of a Grignard reagent on an ester is usual but it has been recorded in a few instances in which the ester bears a tertiary amino-substituent, *e.g.*, the isolation of a small quantity of ketone from the reaction between ethyl β-piperidinopropionate and phenylmagnesium bromide was described in Part I (*loc. cit.*); Prelog and Hanonsek (*Chem. Abs.*, 1931, **25**, 4525) obtained 1-dimethylaminohexan-4-one as well as 6-dimethylamino-3-ethylhexan-3-ol from ethylmagnesium bromide and ethyl γ-dimethylaminobutyrate; recently it has been claimed that ketones are formed exclusively from Grignard reagents and 4-carbalkoxy-4-phenyl-1-methylpiperidines (B.P. 614,567).

2-β-Piperidinopropionylthiophen (III) (also preparable by the Mannich reaction; Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 451) on further reaction with 2-thienylmagnesium bromide (3 mols.) gave the amino-carbinol in 31% yield. A similar reaction between 2-β-piperidino*iso*butyrylthiophen and phenylmagnesium bromide to give 3-piperidino-1-phenyl-1-2′-thienyl-2-methylpropan-1-ol is described in B.P. Appl. 2255/47; Berger, Ziering, and Lee (*J. Org. Chem.*, 1946, **12**, 904) describe the preparation of 4-hydroxy-4-2′-thienyl-1-butylpiperidine from 2-thienyl-lithium and 1-butyl-4-piperidone.

The 2-aminoalkane-carboxylic esters (II) (Table I) required as starting materials were conveniently prepared by addition of an amine to the appropriate substituted acrylic ester. This method has already been used for the preparation of a series of ethyl β-aminopropionates (Part I, *loc. cit.*) and of some ethyl β-aminobutyrates (Philippi and Spenner, *Monatsh.*, 1915, **36**, 97; Philippi and Galter, *ibid.*, 1929, **51**, 253; Morsch, *ibid.*, 1932, **60**, 50). The method has now been successfully applied to a series of methyl and ethyl β-aminobutyrates (II; R = Me, Et; R′ = Me) many of which are new, and to ***methyl*** and ***ethyl*** ***β-dimethylamino-*** and ***β-piperidino-valerate*** and -***δ-methylvalerate*** and the corresponding ***hexoates*** (II; R = Me, Et, R′ = Et, Pr^n, Pr^i, NR″R‴ = NMe$_2$, N<C$_5$H$_{10}$). Some of the higher homologues were unstable and decomposed when kept at room temperature for short periods.

Dehydration of the amino-carbinols furnished the corresponding 3-*amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes* (IV). The method of dehydration employed for the related diphenyl compounds (Part I, *loc. cit.*), namely, boiling under reflux in a mixture of acetic and hydrochloric acids, was successfully applied to the amino-propanols (I; R = H). The homologues (I; R = Me, Et, Pr^n, Pr^i), however, suffered considerable degradation with tar formation under these conditions, but warming with the mixed acids for a limited time on the steam-bath was usually satisfactory. In one example, dehydration was effected by warming in hydrochloric acid alone. 3-Amino-1 : 1-di-2′-thienylbut-1-ene, like the analogous diphenylallylamine (Part I, *loc. cit.*), was unstable, and it was necessary to employ milder conditions in its preparation from the amino-carbinol. The alkenylamines (Table III), which were purified by distillation under reduced pressure, were mobile liquids which became highly coloured on exposure to air; they were converted into water-soluble crystalline ***hydrochlorides***, and some into ***methiodides***.

The pharmacological properties of these compounds, which have been studied by Dr. A. C. White and Mr. A. F. Green of the Biological Division of these Laboratories, were of considerable interest. High antispasmodic activity was shown by several amino-carbinols, *e.g.*, the activity of (I; R = H, NR′R″ = N<C$_5$H$_{10}$) was favourable in relation to synthetic spasmolytics now in clinical use. The majority of the amino-carbinols were powerful local anæsthetics. A number of tertiary amino-butenes, in particular (IV; R = Me, NR′R″ = NMe$_2$, NEt$_2$, N<C$_4$H$_8$, N<C$_5$H$_{10}$), were potent analgesics, as active as morphine in the rat, with undesirable side-effects (in the dog) at a minimum; the alkenylamines (IV) in general also exhibited spasmolytic, antihistamine, and local anæsthetic activity. The detailed pharmacology will be reported elsewhere; a preliminary communication has been published (Adamson and Green, *Nature*, 1950, **165**, 122).

Our investigations in this series are being extended.

EXPERIMENTAL.

(M. p.s are uncorrected.)

2-*Aminoalkanecarboxylic Esters* (see Table I).—*β-Aminopropionates* (II; R′ = H). Ethyl β-dimethylamino-, β-diethylamino-, β-pyrrolidino-, and β-piperidino-propionates (II; R = Et, R′ = H, NR″R‴ = NMe$_2$, NEt$_2$, N<C$_4$H$_8$, N<C$_5$H$_{10}$) were prepared as described in Part I (*loc. cit.*).

β-Aminobutyrates (II; R′ = Me). Methyl or ethyl crotonate was added to the amine (1 mol.) under the various conditions described below, and the esters were isolated from the product by fractional distillation under reduced pressure. The results, and references to earlier syntheses, are summarised in Table I.

Method A. The primary amino-ester (II; R = Et, R′ = Me, R″ = R‴ = H) was prepared by mixing ethyl crotonate (100 g.) with ethanolic ammonia (400 c.c.; saturated at 15°) and heating in an autoclave for 7 hours at 105—110°.

Method B. The amine, dissolved in an equal volume of ethanol, was mixed with methyl or ethyl crotonate, and the product distilled after being kept for 14 days.

Method C. A mixture of the amine and ethyl crotonate was boiled under reflux for 3 hours.

Method D. In the preparation of ***methyl β-pyrrolidinobutyrate*** (II; R = R′ = Me, NR″R‴ = N<C$_4$H$_8$)

sufficient heat to cause boiling of the mixture was generated when pyrrolidine was mixed with methyl crotonate. The mixture was allowed to cool and was distilled after being kept overnight.

TABLE I.

2-Aminoalkane carboxylic esters, $CO_2R{\cdot}CH_2{\cdot}CHR'{\cdot}NR''R'''$.

R.	R′.	NR″R‴.	Method.	Yield, %.	B. p. (mm.).	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
Et	Me	NH_2	A	58	63—64° (12) [a]	—	—	—	—	—	—	—
,,	,,	NHMe	B	70	66—68 (12) [b]	—	—	—	—	—	—	—
,,	,,	NHEt	,,	78	77—79 (12) [c]	—	—	—	—	—	—	—
,,	,,	$NHBu^n$	,,	80	100 (17)	$C_{10}H_{21}O_2N$	63·4	10·7	7·5	64·2	11·2	7·5
,,	,,	,,	C	42	—	—	—	—	—	—	—	—
Me	,,	NMe_2	B	79	66 (17)	$C_7H_{15}O_2N$	57·5	10·0	9·4	57·9	10·3	9·7
Et	,,	,,	,,	75	178—180 [c]	—	—	—	—	—	—	—
Me	,,	NEt_2	,,	57	84 (18)	$C_9H_{19}O_2N$	61·8	11·3	8·5	62·4	11·0	8·1
Et	,,	,,	,,	85	91—92 (18) [b]	—	—	—	—	—	—	—
Me	,,	NPr^n_2	,,	40	116—118 (15)	$C_{11}H_{23}O_2N$	66·0	11·5	7·1	65·7	11·4	7·0
,,	,,	NBu^n_2	,,	29	134—136 (15)	$C_{13}H_{27}O_2N$	68·1	11·8	6·4	68·1	11·8	6·1
Et	,,	$NMe{\cdot}CH_2Ph$	C	41	156—158 (16)	$C_{14}H_{21}O_2N$	71·7	8·7	6·4	71·5	8·9	6·0
Me	,,	$N{<}C_4H_8$	D	89	100—102 (23)	$C_9H_{17}O_2N$	62·8	9·9	8·6	63·2	9·9	8·2
Et	,,	$N{<}C_5H_{10}$	C	85	110—114 (13) [d]	—	—	—	—	—	—	—
,,	,,	$N{<}[CH_2]_4{>}O$	,,	42	121—122 (12)	$C_{10}H_{19}O_3N$	59·3	9·2	7·3	59·7	9·5	7·0
Me	Et	NMe_2	E	50	78—80 (18)	$C_8H_{17}O_2N$	60·1	10·6	8·9	60·4	10·7	8·8
,,	,,	,,	F	83	—	—	—	—	—	—	—	—
Et	,,	,,	,,	85	88—90 (20)	$C_9H_{19}O_2N$	61·9	10·5	7·9	62·4	11·0	8·1
Me	,,	$N{<}C_5H_{10}$	E	65	122—123 (21)	$C_{11}H_{21}O_2N$	66·5	10·3	6·9	66·3	10·6	7·0
,,	,,	,,	F	76	—	—	—	—	—	—	—	—
Et	,,	,,	,,	73	130—132 (21)	$C_{12}H_{23}O_2N$ *	67·2	10·4	6·8	67·6	10·8	6·6
Me	Pr^n	NMe_2	,,	74	90 (15)	$C_9H_{19}O_2N$	62·7	10·7	8·2	62·4	11·0	8·1
Et	,,	,,	,,	83	116—118 (24)	$C_{10}H_{21}O_2N$ *	64·3	10·7	7·3	64·2	11·2	7·5
Me	,,	$N{<}C_5H_{10}$	,,	69	140—141 (22)	$C_{12}H_{23}O_2N$ *	67·6	10·7	6·8	67·6	10·8	6·6
Et	,,	,,	,,	49	158—160 (30)	$C_{13}H_{25}O_2N$ *	—	—	—	—	—	—
Me	Pr^i	NMe_2	,,	69	86—88 (24)	$C_9H_{19}O_2N$	62·6	10·7	7·8	62·4	11·0	8·1
Et	,,	,,	,,	72	108—110 (25)	$C_{10}H_{21}O_2N$ *	—	—	—	—	—	—
Me	,,	$N{<}C_5H_{10}$	,,	29	130—133 (22)	$C_{12}H_{23}O_2N$ *	—	—	—	—	—	—
Et	,,	,,	,,	26	140—141 (17)	$C_{13}H_{25}O_2N$ *	—	—	—	—	—	—

[a] Philippi and Spenner, *Monatsh.*, 1915, **36**, 97. [b] Morsch, *Monatsh.*, 1932, **60**, 50. [c] Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412. [d] Philippi and Galter, *Monatsh.*, 1929, **51**, 253.

* Decomposes on storage.

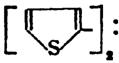
β-Amino-esters.—Higher homologues (II; R′ = Et, Pr^n, Pr^i). β-Ethyl-, β-*n*-propyl-, and β-*iso*propylacrylic acids were prepared by known methods (von Auwers, *Annalen*, 1923, **432**, 74) and were esterified with boiling methanol or ethanol and concentrated sulphuric acid. The methyl esters appear to be new: *methyl β-ethylacrylate*, b. p. 144—145° (Found: C, 63·1; H, 8·9. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%), *methyl β-*n*-propylacrylate*, b. p. 62—64°/22 mm. (Found: C, 65·7; H, 9·5. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%), *methyl β-*iso*propylacrylate*, b. p. 60—62°/22 mm. (Found: C, 65·4; H, 9·6%).

Methyl β-dimethylamino- and *β-piperidino-valerates* (II; R = Me, R′ = Et, NR″R‴ = NMe_2, $N{<}C_5H_{10}$) were prepared by mixing methyl β-ethylacrylate with the amine (1 mol.) in an equal volume of ethanol, and the product was distilled after 4 days (method E). Higher yields were obtained when 1·5 mols. of the amine were used (method F), and accordingly these conditions were employed in the preparation of *methyl* and *ethyl β-dimethylamino-* and *β-piperidino-valerates*, and -δ-methylvalerates and the corresponding *hexoates* (II; R = Me, Et, R′ = Et, Pr^n, Pr^i, NR″R‴ = NMe_2, $N{<}C_5H_{10}$).

Preparation of Amino-carbinols by Means of 2-Thienyl-lithium.—The 3-*amino-* and *N*-substituted 3-*amino-*1 : 1-*di*-2′-*thienylalkan*-1-*ols* (I) (Table II) were prepared from 2-thienyl-lithium and the appropriate β-amino-ester, the general method employed being illustrated by the example described below. As indicated in Table II, the preparation of three carbinols was repeated, with the difference that the 2-thienyl-lithium was prepared from *n*-butyl-lithium (Gilman and Shirley, *J. Amer. Chem. Soc.*, 1949, **71**, 1870); the yields were very similar to, and the products identical with, those obtained by the general method as given in the example.

3-*Dimethylamino*-1 : 1-*di*-2′-*thienylbutan*-1-*ol* (I; R = R′ = R″ = Me). A slow stream of dry nitrogen was led into the apparatus throughout the reaction in order to maintain an inert atmosphere. Thiophen (50 g., 0·6 mol.) in ether (50 c.c.) was added to an ethereal solution of phenyl-lithium prepared from bromobenzene (94 g., 0·6 mol.), lithium (8·5 g., 1·2 atoms), and ether (400 c.c.), and the mixture boiled under reflux for 2 hours. Ethyl β-dimethylaminobutyrate (32·0 g., 0·2 mol.) in ether (50 c.c.) was then added gradually to the mixture, stirred and cooled at −20°. Stirring was continued for 1 hour at room temperature and the mixture, from which a fawn-coloured solid had separated, was kept overnight. Ice (100 g.) was added with stirring, followed by glacial acetic acid until the solution was acidic to litmus. The crude amino-carbinol hydrobromide which separated as a brown crystalline solid was filtered off and washed with ether. The salt was suspended in chloroform, excess of ammonia added with shaking, the chloroform layer separated, washed with water, and dried (Na_2SO_4), and the chloroform evaporated. The residual dark brown oil (46 g.) rapidly crystallised; it was dissolved in boiling light petroleum (500 c.c.; b. p. 40—60°), and the solution filtered from black amorphous material and evaporated to *ca.* 120 c.c. The amino-carbinol crystallised on cooling and had m. p. 85—88° (40 g., 71% yield). Recrystallisation from ethanol gave 36 g., m. p. 90—91°, unchanged by further crystallisations.

TABLE II.

3-*Amino*-1 : 1-*di*-2′-*thienylalkan*-1-*ols*,

$:C(OH)\cdot CH_2\cdot CHR\cdot NR'R''$.

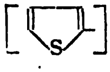
R.	NR′R″.	Yield, %.	M. p.†	Formula.†	Found, %.					Required, %.				
					C.	H.	N.	S.	Cl or I.	C.	H.	N.	S.	Cl or I.
H	NMe_2	72[a]	136—137°	$C_{13}H_{17}ONS_2$	58·4	6·4	5·0	23·8	—	58·5	6·4	5·2	24·0	—
			170—171 *	$C_{13}H_{17}ONS_2,C_2H_2O_4$	50·6	5·5	—	—	—	50·4	5·3	—	—	—
,,	,,	18[b]	65	$C_{15}H_{21}ONS_2$	60·9	7·2	4·6	21·3	—	61·0	7·1	4·7	21·7	—
			196—197 *	$C_{15}H_{21}ONS_2,HCl$	—	—	—	19·0	10·9	—	—	—	19·3	10·7
			193—194 *	$C_{16}H_{24}ONS_2I$	—	—	—	14·7	28·9	—	—	—	14·6	29·1
,,	$N<C_4H_8$	73	118—119	$C_{15}H_{19}ONS_2$	61·5	6·2	4·6	21·6	—	61·4	6·5	4·8	21·8	—
			196—197 *	$C_{15}H_{19}ONS_2,HCl$	—	—	—	19·3	10·8	—	—	—	19·4	10·8
			179—180 *	$C_{16}H_{22}ONS_2I$	—	—	—	14·3	29·4	—	—	—	14·7	29·2
,,	$N<C_5H_{10}$	66	70—72	$C_{16}H_{21}ONS_2$	62·7	6·8	4·8	21·0	—	62·5	6·8	4·6	20·8	—
			(b. p. 176—180/0·04 mm.)											
			198 *	$C_{16}H_{21}ONS_2,HCl$	—	—	—	—	10·4	—	—	—	—	10·3
			188—189 *	$C_{17}H_{24}ONS_2I$	—	—	—	14·1	28·1	—	—	—	14·3	28·3
Me	NH_2	34	126—127	$C_{12}H_{15}ONS_2$	56·9	6·1	5·3	25·0	—	56·9	5·9	5·5	25·3	—
			151—152 *	$C_{12}H_{15}ONS_2,\frac{1}{2}C_2H_2O_4$	52·1	5·3	—	—	—	52·4	5·4	—	—	—
,,	NHEt	24	80—81	$C_{14}H_{19}ONS_2$	60·3	6·6	4·9	22·6	—	59·8	6·8	5·0	22·8	—
			(b. p. 139—143/0·1 mm.)											
			204—205 *	$C_{14}H_{19}ONS_2,\frac{1}{2}C_2H_2O_4$	55·6	6·2	—	—	—	55·2	6·1	—	—	—
,,	NHBu	40	63—64	$C_{16}H_{23}ONS_2$	62·4	7·3	4·7	21·1	—	62·1	7·4	4·5	20·7	—
			183—184 *	$C_{16}H_{23}ONS_2,\frac{1}{2}C_2H_2O_4$	57·5	6·8	—	—	—	57·6	6·8	—	—	—
,,	NMe_2	71	90—91	$C_{14}H_{19}ONS_2$	60·1	6·9	4·8	22·7	—	59·8	6·8	5·0	22·8	—
			198—199 *	$C_{14}H_{19}ONS_2,HCl$	—	—	—	—	11·3	—	—	—	—	11·2
			189 *	$C_{15}H_{22}ONS_2I$	—	—	—	—	29·8	—	—	—	—	30·0
,,	NEt_2	79	75—76	$C_{16}H_{23}ONS_2$	62·1	7·3	4·4	21·1	—	62·1	7·4	4·5	20·7	—
			117—118	$C_{16}H_{23}ONS_2,C_2H_2O_4$	54·5	6·3	—	—	—	54·1	6·3	—	—	—
,,	NPr^n_2	70	91—92	$C_{18}H_{27}ONS_2$	64·0	8·0	4·2	18·9	—	64·1	8·0	4·2	19·0	—
			100	$C_{18}H_{27}ONS_2,C_2H_2O_4$	56·2	6·7	—	—	—	56·2	6·8	—	—	—
,,	$NMe\cdot CH_2Ph$	56	73—74	$C_{20}H_{23}ONS_2$	67·6	6·2	3·9	17·6	—	67·2	6·4	3·9	17·9	—
			143—144 *	$C_{20}H_{23}ONS_2,C_2H_2O_4$	59·3	5·7	—	—	—	59·1	5·6	—	—	—
,,	$N<C_4H_8$	77	88—89	$C_{16}H_{21}ONS_2$	62·8	7·0	4·6	20·9	—	62·5	6·8	4·6	20·9	—
			172—173 *	$C_{16}H_{21}ONS_2,C_2H_2O_4$	54·3	5·9	—	16·0	—	54·4	5·8	—	16·1	—
,,	$N<C_5H_{10}$	55[a]	82—83	$C_{17}H_{23}ONS_2$	63·6	7·2	4·5	19·6	—	63·6	7·2	4·4	19·9	—
			(b. p. 146—148/0·02 mm.)											
			166—167 *	$C_{17}H_{23}ONS_2,C_2H_2O_4$	55·6	6·2	—	—	—	55·5	6·1	—	—	—
,,	$N<[CH_2]_4>O$	48	105—106	$C_{16}H_{21}O_2NS_2$	59·4	6·4	4·3	19·8	—	59·4	6·5	4·3	19·8	—
			134—135 *	$C_{16}H_{21}O_2NS_2,C_2H_2O_4$	52·7	5·9	—	—	—	52·3	5·6	—	—	—
Et	NMe_2	73[a]	83—84	$C_{15}H_{21}ONS_2$	61·0	7·1	4·7	21·3	—	61·0	7·1	4·7	21·7	—
			170—171 *	$C_{15}H_{21}ONS_2,C_2H_2O_4$	53·1	5·9	—	—	—	53·0	6·0	—	—	—
Pr^n	,,	43	—	$C_{16}H_{23}ONS_2$	62·4	7·1	4·4	20·8	—	62·1	7·4	4·5	20·7	—
			(b. p. 145—147/0·05 mm.)											
			138—139 *	$C_{16}H_{23}ONS_2,C_2H_2O_4$	54·3	6·3	—	—	—	54·1	6·3	—	—	—
Pr^i	,,	71	56—57	$C_{16}H_{23}ONS_2$	62·2	7·1	4·5	20·8	—	62·1	7·4	4·5	20·7	—
			125—126	$C_{16}H_{23}ONS_2,C_2H_2O_4$	54·2	6·1	—	15·9	—	54·1	6·3	—	16·0	—

[a] 2-Thienyl-lithium prepared from *n*-butyl-lithium. [b] Prepared by the Grignard reaction.

* M. p. with decomposition. † The m. p. and formula of the base are given first, followed by those of its derivatives.

Preparation of Amino-carbinols by the Grignard Reaction.—3-*Piperidino*-1 : 1-*di*-2′-*thienylpropan*-1-*ol* (I; R = H, NR′R″ = $N<C_5H_{10}$). Ethyl β-piperidinopropionate (37 g., 0·2 mol.) in ether (50 c.c.) was added gradually to an ethereal solution of the Grignard reagent made from 2-bromothiophen (98 g., 0·6 mol.) and magnesium (14·6 g., 0·6 atom) in ether (50 c.c.), stirred and cooled in a bath at 0°. The mixture, from which a heavy oil had separated, was boiled under reflux for 5 hours and kept overnight at room temperature. Crushed ice (100 g.) was added, followed by aqueous ammonium chloride (25%; 100 c.c.). Acetic acid was then added gradually with stirring until the solution was acid to litmus, and the cream-coloured solid which separated was filtered off and washed with ether. The solid was dissolved in chloroform and shaken with excess of ammonia; the chloroform layer was washed with water and dried (Na_2SO_4), and the chloroform evaporated. The residual brown mobile oil was distilled at 0·1 mm. pressure and the following fractions collected: (1) b. p. <160°, 16·5 g., (ii) b. p. 160—188°, 2·0 g., (iii) b. p. 188—194°, 15·3 g., and (iv) b. p. >194°, approx. 10 g. (resinous). Fraction (iii) which rapidly crystallised was the amino-carbinol, m. p. 70—72° after recrystallisation from ethanol (yield 24%). Redistillation of fraction (i) gave, besides some low-boiling material, a mobile liquid, b. p. 102—105°/0·03 mm. (10·1 g., 23%), which was identified as 2-β-piperidinopropionylthiophen (III) [hydrochloride (recrystallised from methanol), m. p. 203—205°, not depressed by a specimen prepared by the Mannich reaction (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 451)].

TABLE III.

3-*Amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes*,  :C:CH·CHR·NR′R″

		Base.	Hydrochloride.					
					Found, %.		Reqd., %.	
R.	NR′R″.	B. p. (mm.).	M. p.	Formula.	Cl.	S.	Cl.	S.
H	NMe_2	91—94° (0·05)	144—145°	$C_{13}H_{15}NS_2,HCl$	12·5	22·7	12·4	22·4
,,	NEt_2	—	116—117	$C_{15}H_{19}NS_2,HCl$	11·5	19·8	11·3	20·4
,,	$N<C_4H_8$	—	102—103	$C_{15}H_{17}NS_2,HCl$	11·3	20·3	11·4	20·5
,,	$N<C_5H_{10}$	143 (0·05) [a]	171—173 *	$C_{16}H_{19}NS_2,HCl$	10·9	19·8	10·9	19·7
Me	NH_2	—	174—175 *	$C_{12}H_{13}NS_2,HCl$	12·8	23·2	13·1	23·2
,,	NHEt	112—114 (0·03)	134—135	$C_{14}H_{17}NS_2,HCl$	11·9	21·3	11·8	21·4
,,	NHBu	122—124 (0·04) [b]	123—124	$C_{16}H_{21}NS_2,HCl$	11·2	19·8	10·8	19·5
,,	NMe_2	123—125 (0·05)	169—170	$C_{14}H_{17}NS_2,HCl$	12·1	22·0	11·8	21·4
,,	NEt_2	122—128 (0·03)	152—153	$C_{16}H_{21}NS_2,HCl$	10·6	19·5	10·8	19·5
,,	NPr^n_2	119—121 (0·01)	112—115 [c]	$C_{18}H_{25}NS_2,HCl$	10·0	17·8	10·0	18·0
,,	$NMe{\cdot}CH_2Ph$	146—148 (0·01)	160—161 *	$C_{20}H_{21}NS_2,HCl$	9·6	16·3	9·5	17·0
,,	$N<C_4H_8$	132—135 (0·1)	167—169	$C_{16}H_{19}NS_2,HCl$	10·9	19·5	10·9	19·7
,,	$N<C_5H_{10}$	132—136 (0·05)	188—189	$C_{17}H_{21}NS_2,HCl$	10·5	18·6	10·5	18·9
,,	$N<[CH_2]_4>O$	130—136 (0·05)	181—182	$C_{16}H_{19}ONS_2,HCl$	10·4	18·4	10·4	18·7
Et	NMe_2	110—112 (0·03)	138—139	$C_{15}H_{19}NS_2,HCl$	11·5	20·3	11·3	20·4
Pr^n	,,	116—118 (0·03)	158—159	$C_{16}H_{21}NS_2,HCl$	10·8	19·6	10·8	19·5
Pr^i	,,	107—109 (0·03) [d]	(159—160 *) [e]	—	—	—	—	—

[a] Found: C, 66·7; H, 6·4; N, 4·7; S, 22·4. $C_{16}H_{19}NS_2$ requires C, 66·4; H, 6·6; N, 4·8; S, 22·2%. [b] Found: C, 66·0; H, 7·2; N, 4·8; S, 22·0. $C_{16}H_{21}NS_2$ requires C, 66·0; H, 7·2; N, 4·8; S, 22·0%. [c] Found, for hydrate: H_2O, 2·3. $C_{18}H_{25}NS_2,HCl,\frac{1}{2}H_2O$ requires H_2O, 2·5%. [d] Found: C, 66·0; H, 7·3; N, 4·8; S, 22·0. $C_{16}H_{21}NS_2$ requires C, 66·0; H, 7·2; N, 4·8; S, 22·0%. [e] Found, for hydrogen oxalate: S, 16·7. $C_{16}H_{21}NS_2,C_2H_2O_4$ requires S, 16·8%.

* M. p. with decomposition.

The amino-carbinol was also prepared from 2-β-piperidinopropionylthiophen hydrochloride (0·1 mol.) and 2-thienylmagnesium bromide (0·3 mol.) under conditions similar to those described above, a yield of 31% being obtained.

3-*Diethylamino*-1 : 1-*di*-2′-*thienylpropan*-1-*ol* (I; R = H, R′ = R″ = Et). The amino-carbinol was obtained in 18% yield from the reaction between 2-thienyl-lithium (0·3 mol.) and ethyl β-diethylaminopropionate (0·1 mol.) under conditions similar to those described above for the piperidino-analogue. In this example also a considerable quantity of a low-boiling fraction was obtained when the crude product was distilled under reduced pressure, but on redistillation it boiled over a wide range with some decomposition.

The amino-carbinols were purified by recrystallisation from ethanol; in those examples for which a b. p. is recorded in Table II, the crude products were given a preliminary purification by fractional distillation under reduced pressure.

The *hydrochlorides* were prepared by passing dry hydrogen chloride into a solution of the base in chloroform at 0° until neutrality was reached. The salts crystallised on the addition of ether and were recrystallised from ethanol.

The oxalates were prepared by mixing the base (1 mol.) in ethanol with anhydrous oxalic acid (1 mol.) in ethanol at room temperature. The salts which rapidly separated were recrystallised from ethanol. Under these conditions the primary and secondary amino-carbinols gave neutral *oxalates*, and the tertiary amines *hydrogen oxalates*.

The *methiodides* were prepared by adding methyl iodide (2 mols.) to a solution of the tertiary amino-carbinols in a small volume of acetone After several hours, the salts which had separated were recrystallised from methanol.

Dehydration of Amino-carbinols.—The method described for the dehydration of the related diphenyl-carbinols (Part I, *loc. cit.*) was successfully applied to the aminopropanols (I; R = H), the yields of distilled allylamine being approx. 70% (example 1). When this method was applied to some amino-butanols (I; R = Me), however, extensive degradation occurred and black amorphous solids were formed (example 2). The amino-butanols and higher homologues were therefore dehydrated under milder conditions, whereby the unsaturated amines were obtained usually in yields of 70—90% (example 3). In the preparation of 3-*benzylmethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = R′ = Me, R″ = CH_2Ph) by this method considerable quantities of tar were produced, and the yield was 40%. 3-Amino-1 : 1-di-2′-thienylbutan-1-ol (I; R = Me, R′ = R″ = H) was completely decomposed to tarry products by this method, and therefore dehydration was effected under milder conditions as described in example 4. Dehydration by warming of the carbinol with hydrochloric acid alone was successful in the preparation of 3-*diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = Me, R′ = R″ = Et) (example 5).

Example 1. 3-Dimethylamino-1 : 1-di-2′-thienylpropan-1-ol (15 g.) was dissolved in a mixture of concentrated hydrochloric acid (30 c.c.) and glacial acetic acid (100 c.c.), and the solution boiled under reflux for 20 minutes. The deeply coloured solution was then concentrated under reduced pressure, the residue treated with excess of ammonia, and the base extracted with ether. The ethereal solution was dried (Na_2SO_4), the ether evaporated, and the residue distilled under reduced pressure. The product, 3-*dimethylamino*-1 : 1-*di*-2′-*thienylprop*-1-*ene* (IV; R = H, R′ = R″ = Me), was a colourless mobile liquid which became purple on exposure to air and had b. p. 91—94°/0·05 mm. (yield 9·9 g., 71%).

Example 2. 3-Dimethylamino-1 : 1-di-2′-thienylbutan-1-ol (15 g.) was boiled under reflux in acidic solution as described in example 1. A black solid was deposited on the walls of the flask. The mixture was concentrated under reduced pressure and filtered. The residue was a black intractable solid (melting between 135° and 180°), insoluble in boiling water or aqueous mineral acids; the dark filtrate gave a small amount of tarry material when basified.

Example 3. 3-Piperidino-1 : 1-di-2′-thienylbutan-1-ol (20 g.) was warmed on the steam-bath for 15 minutes with concentrated hydrochloric acid (40 c.c.) and glacial acetic acid (130 c.c.). The solution was worked up as described in example 1 (care being taken to keep the temperature low during the concentration of the solution), and the product, 3-*piperidino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = Me, NR′R″ = $N<C_5H_{10}$), was distilled under reduced pressure, having b. p. 132—136°/0·05 mm. (yield 14·5 g., 78%).

Example 4. Dry hydrogen chloride was led into a cooled solution of 3-amino-1 : 1-di-2′-thienylbutan-1-ol (1·6 g.) in chloroform (8 c.c.). The white solid which separated quickly dissolved, the solution became pale brown, and drops of water separated. The chloroform solution was dried (Na_2SO_4) and evaporated under reduced pressure to small volume, and ether added gradually until crystallisation commenced. 3-*Amino*-1 : 1-*di*-2′-*thienylbut*-1-*ene hydrochloride* (IV; R = Me, R′ = R″ = H) was obtained as fawn-coloured crystals, m. p. 174—175° (decomp.).

Example 5. 3-Diethylamino-1 : 1-di-2′-thienylbutan-1-ol (15 g.) was added to hydrochloric acid (6N.; 75 c.c.), and the mixture heated on the steam-bath for 15 minutes. The resulting deeply coloured solution was cooled, excess of ammonia added, and the base extracted with chloroform. The chloroform was evaporated, and the residual oil distilled under reduced pressure to give 3-*diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = Me, R′ = R″ = Et), b. p. 122—128°/0·03 mm. (10·5 g., 74%).

The 3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes* and their *hydrochlorides* are recorded in Table III. The hydrochlorides, prepared in a similar manner to those of the amino-carbinols, were recrystallised from ethanol–ethyl acetate. In some cases the hydrochlorides were also isolated directly from the dehydration mixture by evaporation to dryness and recrystallisation of the solid residue.

The following methiodides were prepared by mixing the base with excess of methyl iodide in acetone solution. After several hours, the product was filtered off and recrystallised from methanol. 3-*Diethylamino*-1 : 1-*di*-2′-*thienylprop*-1-*ene methiodide*, m. p. 174—175° (decomp.) (Found: I, 31·0. $C_{16}H_{22}NIS_2$ requires I, 30·3%); 3-*pyrrolidino*-1 : 1-*di*-2′-*thienylprop*-1-*ene methiodide*, m. p. 186° (decomp.) (Found: I, 30·0. $C_{16}H_{20}NIS_2$ requires I, 30·5%); 3-*piperidino*-1 : 1-*di*-2′-*thienylprop*-1-*ene methiodide*, m. p. 193—194° (decomp.) (Found: I, 29·3. $C_{17}H_{22}NIS_2$ requires I, 29·5%); 3-*dimethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene methiodide*, decomposes from 130° (Found: I, 32·3. $C_{15}H_{20}NIS_2$ requires I, 31·4%).

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CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT.

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181. *Reactions of Ethylene Oxides. Part IV. The Reaction of Epichlorohydrin with Some Aromatic Amines.*

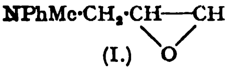
By W. DAVIES and W. E. SAVIGE.

Epichlorohydrin with one mole or two moles of methylaniline gives good yields of 1-chloro-3-*N*-methylanilinopropan-2-ol (II) and 1 : 3-di-(*N*-methylanilino)propan-2-ol, respectively. Modification of the conditions brings about the production of dimethylaniline, 1-methyltetrahydroquinoline, and 3-hydroxy-1-methyltetrahydroquinoline (which readily loses water to form 1-methyl-1 : 2-dihydroquinoline). The basic group in the oxide derived from the chlorohydrin (II) has little effect on its general properties and reactions, which are essentially those of a normal αβ-oxide.

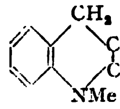
REACTION of methylaniline and epichlorohydrin, described chiefly in the patent literature, has been reinvestigated in order to prepare, and examine the properties of, a compound such as

3-*N*-methylanilinopropylene oxide (I) containing a basic centre separated by one methylene group from an αβ-oxide ring. The reaction is found to give a variety of products depending on the experimental conditions. For example, Eisleb (D.R.-P. 473,219/1929; U.S.P. 1,790,042/1931) obtained (I) by interaction of equimolar quantities of epichlorohydrin and methylaniline in aqueous alcohol, followed by treatment with alkali. On the other hand, Lange (D.R.-P. 619,825) obtained 3-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline (III) when the reaction was carried out in chlorobenzene. It is now found that in hot aqueous alcohol or in boiling xylene the chief product is 1-*chloro*-3-N-*methylanilinopropan*-2-*ol* (II), which is converted by alkali into the oxide (I).

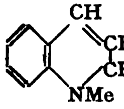
Further differences are found when the condensation occurs in the absence of solvent and when the temperature is varied. 1 : 3-Di-(*N*-methylanilino)propan-2-ol was the only pure compound isolated, and that in very small yield, by Wedekind and Bruch (*Annalen*, 1929, **471**, 94) from equimolar amounts of reactants without a solvent, on the water-bath. This diamine is now found to be produced almost quantitatively from two moles of methylaniline at rather higher temperatures, a process which recalls the formation of 1 : 3-dianilinopropan-2-ol from epichlorohydrin and aniline (Fouconnier, *Compt. rend.*, 1888, **107**, 250; Fukagawa, *Ber.*, 1935, **68**, *B*, 1344).


$\mathrm{NPhMe{\cdot}CH_2{\cdot}\underset{\diagdown\,O\,\diagup}{CH{-}CH_2}}$ (I.)

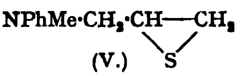
$\mathrm{NPhMe{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2Cl}$ (II.)

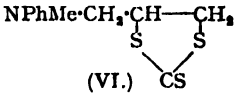


(III.)



(IV.)


$\mathrm{NPhMe{\cdot}CH_2{\cdot}\underset{\diagdown\,S\,\diagup}{CH{-}CH_2}}$ (V.)


$\mathrm{NPhMe{\cdot}CH_2{\cdot}\underset{\underset{CS}{S\quad S}}{CH{-}CH_2}}$ (VI.)

However, if equimolar amounts of the reactants are refluxed without a solvent for a short time, the reaction becomes violently exothermic, and the products, after treatment with concentrated alkali, are dimethylaniline, kairoline (1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline), and 3-hydroxykairoline (III) in yields of 8, 10, and 45% respectively, the remainder consisting of small intermediate fractions and higher-boiling material. If the subsequent alkali treatment is omitted, it is very difficult to separate 3-hydroxykairoline by distillation from the chlorohydrin (II) present in the reaction mixture. When the conditions of the reaction are more controlled, dimethylaniline, the oxide (I), 3-hydroxykairoline (III), and 1 : 3-di-(*N*-methylanilino)propan-2-ol are isolated in yields of 2, 35, 10, and 2% respectively. The kairoline obtained is identified in the usual way. Little information is given by Lange (*loc. cit.*) about the main heterocyclic product 3-hydroxykairoline. It has the high viscosity and boiling point characteristic of tertiary ethanolamine derivatives, and the presence of the hydroxy-group is shown by reaction with methylmagnesium iodide and phenyl *iso*cyanate. The position of the hydroxy-group has not been proved, but the 3-position is to be expected if the nitrogen ring is formed by intramolecular reaction of either (I) or (II). Similarly, 3-hydroxy-1-phenyl-1 : 2 : 3 : 4-tetrahydroquinoline is considered (D.R.-P. 284,291) to be the product from the reaction of epichlorohydrin and diphenylamine under pressure, which, if catalysed by sodium iodide, is now found to occur at ordinary pressure; the presence of the hydroxy-group is shown by the formation of a crystalline *phenylurethane*.

3-Hydroxykairoline is converted by distillation over solid potassium hydroxide into a lower-boiling liquid, 1-*methyl*-1 : 2-*dihydroquinoline* (IV), readily reduced to kairoline by zinc and sulphuric acid. This dihydro-compound, like 1-methyl-2-propyl-1 : 2-dihydroquinoline (von Braun and Aust, *Ber.*, 1914, **47**, 3023), polymerises readily when kept, thus favouring the 1 : 2- rather than the 1 : 4-dihydro-structure.

The mechanism of the production of 3-hydroxykairoline (III) is deduced from known reactions of epichlorohydrin. Thus, in the presence of hydroxylic solvents or at high temperatures, epichlorohydrin generally combines with amines to form first the 1-chloropropan-2-ol, and it has now been confirmed that with an equimolecular quantity of *p*-toluidine it gives the crystalline *p*-tolyl analogue of (II) (Cohn and Friedlander, *Ber.*, 1904, **37**, 3034); Drefus (F.P. 702,553) claims a similar preparation of the α-naphthyl analogue. Lange (U.S.P. 2,150,001/1939) also reports that primary aromatic amines can yield tertiary amines of the type $\mathrm{Ar{\cdot}N[CH_2{\cdot}CH(OH){\cdot}CH_2Cl)_2}$. Thus, methylaniline probably produces initially (II) which then cyclises to (III) with loss of hydrogen chloride. This view is supported by the decomposition of (II) at 180—200°, to give 50% of (III) together with dimethylaniline and a polymer. A similar ring closure is involved in the formation of lilolidine by heating 1-3′-chloropropyldihydroindole (von Braun, Heider, and Wyczatkowska, *Ber.*, 1918, **51**, 1219), and in the mechanism postulated by Lange (I.G. Farbenind., Zetco Reports, Jan., 1946, F.I.A.T. Microfilm Reel C 60, PB L 64079) for the production of 3-hydroxytetrahydroquinoline derivatives from epichlorohydrin and α- or β-naphthylamine or secondary arylalkylamines. Further analogous reactions involving primary and secondary aromatic amines are set out by Lange and Helberger (D.R.-P. 634,038) and Lange (U.S.P. 2,194,399/1940).

The condensation of methylaniline or similar amines with epichlorohydrin to produce kairoline (or analogous bases) and dimethylaniline (or similar amines) is apparently novel, and the mechanism is not yet clearly understood. Dunlop and Jones (*J.*, 1909, **95**, 420) showed that methylaniline was converted into dimethylaniline by methyl bromide which is produced when ethylene dibromide and methylaniline form 1 : 4-diphenylpiperazine. (For similar fissions of alkyl groups attached to nitrogen see Wedekind and Bruch, *loc. cit.*, p. 76, and Thorpe and Wood, *J.*, 1913, **103**, 1611.) The somewhat analogous conversion of methylaniline into dimethylaniline may occur *via* methyl chloride during the condensation with epichlorohydrin, but it is probable that an intermediate compound (*e.g.*, II) undergoes fission at the link between the $N\cdot CH_2$ and the CH(OH). That this link can be unstable in halogen-free compounds related to (II) is shown by the production of dimethylaniline in 50% yield on decomposition of the crude *trithiocarbonate* (VI) by heat. Moreover, the production of dimethylaniline during the inter-action of methylaniline and epichlorohydrin seems to be associated with the formation of kairoline. This and associated reactions are being further investigated.

The oxide (I) has been examined in order to verify its structure, since condensations of epichlorohydrin with certain reagents have been found to give the unsaturated alcohol rather than the expected oxide. Thus, with sodium acetylide epichlorohydrin gives pent-2-en-4-yn-1-ol, $CH⋮C\cdot CH⁚CH\cdot CH_2\cdot OH$ (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1610) and with sodium sulphinates gives sulphones $R\cdot SO_2\cdot CH⁚CH\cdot CH_2\cdot OH$ (Culvenor, Davies, and Savige, *J.*, 1949, 2200) which are also formed by the action of cold dilute alkali on the chloro-alcohols, $R\cdot SO_2\cdot CH_2\cdot CH(OH)\cdot CH_2Cl$. The dioxan type of dimer from the unsaturated alcohol is also sometimes formed, but that possibility is discarded in the case of the methylaniline product, because the latter has great chemical activity and a low boiling point. The following reactions of (I) are characteristic of αβ-oxides, and are unlikely to occur readily with the unsaturated alcohol, $NPhMe\cdot CH⁚CH\cdot CH_2\cdot OH$ unless its double bond is far more reactive than the formula indicates.

Methylaniline gives with (I) the expected crystalline diamine 1 : 3-di-(*N*-methylanilino)-propan-2-ol; Eisleb (*loc. cit.*; also U.S.P. 1,845,403/1932) obtained analogous products from (I) with ammonia and with ethylamine. The oxide (I) is converted by dilute sulphuric acid into the crystalline *glycol*, $NPhMe\cdot CH_2CH(OH)\cdot CH_2\cdot OH$, by sodium sulphite into an *isethionate*, probably $NPhMe\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot SO_3Na$, and by thiourea into the corresponding *sulphide* (V). Potassium methyl xanthate (cf. Culvenor, Davies, and Pausacker, *J.*, 1946, 1051) with (I) forms the corresponding impure trithiocarbonate (VI) characterised as its *picrate*. Finally, the absence of active hydrogen was shown by failure to react with methylmagnesium iodide, and absence of a hydroxy-group by infra-red analysis, indicating that the compound is the oxide (I) and not the unsaturated alcohol.

It is to be expected that salt formation involving the nitrogen in (I) would favour the formation of the unsaturated alcohol, but it has not been possible to obtain a crystalline methyl iodide derivative of (I), and dry hydrogen chloride at 0° yields an oily hydrochloride which cannot be purified and readily isomerises on warming to give a chlorohydrin, probably (II). However, the corresponding sulphide (V) does give a crystalline *monomethiodide*, which is regarded as an ammonium and not a sulphonium salt (cf. Culvenor, Davies, and Heath, *J.*, 1949, 282) and shows evidence of the retention of the thiairene ring. The properties of αβ-oxides containing an electrophilic group are being further studied.

EXPERIMENTAL.

Interaction of Epichlorohydrin with Methylaniline.—1-*Chloro*-3-N-*methylanilinopropan*-2-*ol* (II), a pale yellow viscous liquid, b. p. 132—134°/0·8 mm., 140°/2·5 mm., n_D^{16} 1·572, was obtained when epichlorohydrin (25 ml., 0·32 mol.), methylaniline (25 ml., 0·23 mol.), water (20 ml.), and alcohol (30 ml.) were heated under reflux for 2 hours and then treated with water (20 ml.), the product being extracted with ether, dried, and distilled (Found : C, 61·3, 61·25; H, 7·2, 7·0; N, 7·4. $C_{10}H_{14}ONCl$ requires C, 60·2; H, 7·0; N, 7·0%). The high values for carbon and nitrogen are attributed to slight contamination of the product with 3-hydroxykairoline (III) into which (II) was partly converted at the temperature of distillation. When (II) was redistilled at 167°/15 mm., sufficient (III) was produced to be identified as its methiodide, and the last few viscous drops of the distillate gave the blue coloration in air and other reactions indicative of the presence of dimethylaniline hydrochloride. The chlorohydrin (II), b. p. 152—155°/4·5 mm., was also obtained on refluxing epichlorohydrin (18 ml.) and methylaniline (22 ml.) in xylene (35 ml.) for 6 hours, the product being again contaminated with (III), but no reaction occurred in boiling acetone with or without potassium iodide. Methylmagnesium iodide gave methane by interaction with (II), which yielded no crystalline derivative with picric or picrolonic acid, phenyl *iso*cyanate, methyl iodide, or dry hydrogen chloride.

1 : 3-Di-(*N*-methylanilino)propan-2-ol, b. p. 195—198°/0·25 mm., m. p. 80°, short needles from benzene–light petroleum (Found : C, 76·4; H, 8·25; N, 10·15. Calc. for $C_{17}H_{22}ON_2$: C, 75·6; H, 8·15; N, 10·4%), previously made by Wedekind and Bruch (*loc. cit.*, who record m. p. 82°, b. p. 180—240°/20 mm.), was formed almost quantitatively from methylaniline (2·5 g.) and epichlorohydrin (0·9 g.) at 155° (1 hour) and then 170° (1 hour), the viscous acid product being then dissolved in dilute hydrochloric acid (5 ml.) and treated with aqueous sodium hydroxide.

In the absence of solvents, equimolecular amounts of methylaniline and epichlorohydrin gave 1-methyltetrahydroquinoline derivatives, the formation of which was favoured by high temperatures. Residual viscous material was also produced, and this can be the main product if the temperature of the reaction is too high. The following are typical condensations. (i) Epichlorohydrin (34·8 ml.) was heated under reflux, and methylaniline (43·6 ml.) added in small portions during ½ hour. Five minutes later, an exothermic reaction occurred, the temperature rising to >200°. The mixture was warmed on the water-bath for a further hour, cooled, and stirred with ether and a solution of sodium hydroxide (25 g.) in water (50 ml.) for 1 hour. The dried ethereal extract gave, after two refractionations, the following chlorine-free fractions, together with unchanged epichlorohydrin (5 ml.) and a viscous residue (20 ml.): (*a*) b. p. 74—77°/13 mm. (6 ml.), identified by its picrate as dimethylaniline; (*b*) b. p. 62°/0·15 mm., 243°/756 mm., n_D^{21} 1·585 (8 ml.), kairoline (Found : C, 81·65; H, 9·0; N, 9·7. Calc. for $C_{10}H_{13}N$: C, 81·65; H, 8·85; N, 9·5%), a mobile liquid insoluble in water; and (*c*) b. p. 134—136°/0·18 mm., 290°/760 mm., n_D^{20} 1·595 (35 ml.), 3-hydroxykairoline (III), an extremely viscous liquid for which Lange (D.R.-P. 619,825) gives b. p. 165—166°/12 mm. (Found : C, 73·0, 73·6; H, 7·9, 8·2; N, 8·3. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%).

(ii) Epichlorohydrin (21·8 ml.) and methylaniline (26·2 ml.), after reaction as described above except that adequate external cooling was applied at the onset, were heated at 180° for 1½ hours, to give : (*a*) dimethylaniline, b. p. 82°/12 mm. (1 ml.), which exhibited slight fluorescence; (*b*) 3-*N*-methylanilinopropylene oxide (I), b. p. 140—146°/12 mm. (18 ml.), identified as picrate; (*c*) 3-hydroxykairoline, b. p. 156—161°/12 mm. (5 ml.), identified as picrolonate; and (*d*) 1 : 3-di-(*N*-methylanilino)propan-2-ol, b. p. 195—198°/0·25 mm., m. p. 80°, identified by a mixed m. p. No kairoline was isolated in this case, although formation of a very small amount is not precluded. Much residue was again obtained.

Kairoline was identified as methiodide, m. p. 171·5°, and picrate, m. p. 137·5°, both m. p.s being undepressed on admixture with the respective derivatives of commercial (Schuchardt) material. The m. p. of the picrate of the commercial base could not be raised above 125° by the use of neutral organic solvents, but crystallisation from dilute acetic acid gave material of m. p. 134—135°; the impurity was quinoline, and the presence of this or similar substances may be the reason for the wide variation in the m. p. (125° to 145°) recorded in the literature. 3-Hydroxykairoline with nitrous acid gave an orange colour which changed to green on neutralisation with aqueous ammonia. With methylmagnesium iodide 3-hydroxykairoline gave methane, and with phenyl *iso*cyanate in benzene at 100° (1 hour) gave an uncrystallisable oil. No precipitate was formed on treatment with alcoholic picric acid, but with picrolonic acid a sparingly soluble *picrolonate*, m. p. 185° (decomp.), yellow needles from acetone, was obtained (Found : C, 55·85; H, 4·9. $C_{10}H_{13}ON,C_{10}H_8O_5N_4$ requires C, 56·15; H, 4·9%). Warming the base with excess of methyl iodide gave a *methiodide*, m. p. 157° (slight decomp.) (prisms from acetone–ether) considerably variable according to the rate of heating (Found : C, 43·1; H, 5·35; N, 4·45; I, 41·8. $C_{11}H_{16}ONI$ requires C, 43·3; H, 5·25; N, 4·6; I, 41·65%).

1-*Methyl*-1 : 2-*dihydroquinoline* (IV).—This *base*, b. p. 128°/15 mm., was obtained in theoretical yield when 3-hydroxykairoline (5 g.) was heated with powdered potassium hydroxide (5 g.) in a distilling flask at 190°/20 mm., the distillate being redistilled immediately (Found : C, 83·0; H, 7·65; N, 9·6. $C_{10}H_{11}N$ requires C, 82·7; H, 7·6; N, 9·65%). It is a mobile water-insoluble liquid, aqueous-alcoholic solutions of which fluoresce. It formed a methiodide, m. p. 205° (with sublimation), rapidly developed a red colour, and became cloudy and viscous after 24 hours, even in a sealed tube or in the presence of a trace of quinol. It was not re-formed by heating the viscous material, which partly solidified during 7 days. The polymer was insoluble in alcohol, but acetone dissolved the adhering oil, leaving a white powder which dissolved in hot alcohol and was re-precipitated on cooling. Two repetitions of this treatment gave an amorphous *polymer*, m. p. 100° (Found : C, 82·1; H, 8·0%), which darkened during several days, while the m. p. fell to 94—97°.

Conversion of (IV) *into Kairoline.*—To monomeric (IV) (3 g.) in dilute sulphuric acid (15 ml.) at 100° zinc dust (10 g.) was added in portions during 1½ hours, with occasional shaking. The mixture was filtered, made alkaline with aqueous sodium hydroxide, and extracted with ether. The dried extract on distillation gave a stable mobile liquid, identified as kairoline, b. p. 110°/15 mm. (0·5 g.), by a mixed m. p. determination of its picrate.

Production of 3-Hydroxykairoline from 1-*Chloro*-3-N-*methylanilinopropan*-2-*ol* (II).—The chlorohydrin (II) (5 g.) was heated at 190—200° for 2 hours, gaseous products being evolved. The dark, viscous residue was shaken with a mixture of ether and 5% aqueous sodium hydroxide. The dried ethereal extract yielded dimethylaniline, b. p. 110°/20 mm. (0·5 ml.) (identified as picrate), and 3-hydroxykairoline, b. p. 130—135°/1 mm. (2·5 g.), identified as picrolonate. The remainder was high-boiling material.

Preparation and Reactions of 3-N-*Methylanilinopropylene Oxide.*—The crude undistilled chlorohydrin (II) was converted by cold 50% sodium hydroxide solution into 3-*N*-methylanilinopropylene oxide (I), b. p. 120—122°/3 mm., 107°/0·5 mm., n_D^{19} 1·562 (Found : C, 73·6; H, 7·8; N, 8·8. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 7·95; N, 8·6%), in 74% yield. Eisleb (*loc. cit.*) records b. p. 132—134°/8 mm., 160—162°/30 mm. A 10% yield of 1 : 3-di-(*N*-methylanilino)propan-2-ol was also formed.

The oxide was characterised as *picrate*, m. p. 109°, yellow prisms from alcohol (Found: N, 14·0. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires N, 14·3%), did not produce methane with methylmagnesium iodide, and gave no precipitate with aqueous *p*-nitrophenylhydrazine hydrochloride. Infra-red analysis (for which we thank Dr. J. B. Willis) showed the absence of hydroxy-groups. The product formed on heating (I) (1·63 g.) and methylaniline (1·25 g.) at 160° for 2 hours solidified on cooling; washing the product with light petroleum gave 1 : 3-di-(*N*-methylanilino)propan-2-ol (IV), m. p. 80°, without recrystallisation.

3-N-*Methylanilinopropylene Glycol*.—The *glycol*, b. p. 156—158°/0·5 mm., m. p. 74—75°, plates from benzene–light petroleum, was prepared by heating (I) (5 g.) in 5N-sulphuric acid (10 ml.) under gentle reflux for ½ hour, cooling, and carefully neutralising the mixture with concentrated aqueous ammonia (Found: C, 66·55; H, 8·35. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%). In a first experiment, crystallisation of this glycol, which was difficult to extract from aqueous medium with ether, was effected only after evaporation to dryness and extraction with alcohol–ether, followed by distillation and digestion of the distillate with cold ether; in a second experiment crystallisation was effected by seeding the crude reaction mixture. The glycol was readily soluble in alcohol or benzene, slightly soluble in ether or water, and sparingly so in light petroleum.

Sodium 3-N-*Methylanilino-2-hydroxypropane*-1-*sulphonate*.—This *salt* (Found: Na, 8·65. $C_{10}H_{14}O_4SNa$ requires Na, 8·6%), m. p. 266°, lustrous plates from 90% alcohol, was obtained when the oxide (I) (1·63 g.) in alcohol was mixed with sodium sulphite (3 g.) and the mixture buffered to neutrality (phenolphthalein) with acetic acid and aqueous sodium acetate. The mixture was then kept at 30° for 18 hours and concentrated. This isethionate is readily soluble in water (cf. Lauer and Hill, *J. Amer. Chem. Soc.*, 1936, **58**, 1873).

Attempts to make pure salts, other than the picrate, from (I) were unsuccessful. An uncrystallisable oil was obtained when (I) was heated with excess of methyl iodide for ½ hour. Dry hydrogen chloride was passed into a solution of (I) (1·63 g.) in dry benzene at 0°, with cooling, until the weight had increased by 0·36 g. The mobile oil which separated dissolved by warming to 60° and was not reprecipitated on cooling. Distillation gave a main fraction b. p. 140°/1·2 mm., n_D^{15} 1·572, which contained non-ionic chlorine and was probably the chlorohydrin (II) or an isomer.

N-*Methylanilinomethyl-thiairene*(-*propylene Sulphide*) (V).—This *compound*, a pale yellow liquid, b. p. 107—108°/0·1 mm., 154°/12 mm., n_D^{11} 1·606, possessing a slight offensive odour, was obtained (3 g.) when thiourea (2·5 g.) and (I) (4·1 g.) in methanol (20 ml.) were stirred at 60° for 1¼ hours, the mixture being then poured into water (100 ml.), extracted with chloroform, dried, distilled, and fractionated to remove unchanged oxide (Found: N, 7·7. $C_{10}H_{13}NS$ requires N, 7·8%). It forms a sparingly soluble *picrate*, yellow pyramid-like crystals (from alcohol), m. p. 76·5° (Found: S, 7·8. $C_{10}H_{13}NS,C_6H_3O_7N_3$ requires S, 7·85%). When the sulphide (V) was heated under reflux with a large excess of methyl iodide for 15 minutes, a crystalline *methiodide* was rapidly precipitated, recrystallisation from alcohol–benzene giving plates, m. p. 147·5° (Found: S, 9·9; I, 40·25. $C_{11}H_{16}NIS$ requires S, 9·95; I, 39·6%), soluble in water, but rapidly polymerised when heated in alkali (cf. Dachlauer and Jackel, D.R.-P. 636,708). Nitrogen was readily evolved on treatment of the methiodide with a solution of sodium azide, iodine, and potassium iodide in water.

3-N-*Methylanilinopropylene Trithiocarbonate* (VI).—This was obtained as a viscous, malodorous, non-distillable, yellow oil when the oxide (I) (4·1 g.) and excess of potassium methylxanthate were kept in methyl alcohol for 18 hours. The oil was extracted with benzene, the extract washed well with water and methanol and dried, and the benzene evaporated off. Like most trithiocarbonates, it was only sparingly soluble in alcohol, ether, or acetone, but readily soluble in benzene or chloroform. A benzene solution of the undistilled ester was warmed with an excess of alcoholic picric acid and the reddish oil set aside until crystallisation occurred. Recrystallisation from alcohol, in which it is not very soluble, gave yellow crystals of the *picrate*, m. p. 124—125° (Found: S, 19·9. $C_{11}H_{13}NS_3,C_6H_3O_7N_3$ requires S, 19·85%). On attempted distillation of the ester at 0·6 mm., decomposition occurred at 200°, the distillate consisting mainly of dimethylaniline, as shown by its conversion in high yield by picrolonic acid into *dimethylaniline picrolonate*, small yellow prisms (Found: N, 18·05. $C_8H_{11}N,C_{10}H_8O_5N_4$ requires N, 18·2%), m. p. 200° (from alcohol) not depressed on admixture with the authentic picrolonate.

Reaction of Epichlorohydrin with Diphenylamine.—No reaction occurred when a mixture of these compounds was refluxed without a catalyst. Diphenylamine (16·9 g.), epichlorohydrin (13·9 g.), and sodium iodide (10 g.) were refluxed for 5 hours, cooled, decanted from inorganic material, and distilled, first at 15 mm. whereupon a mixture of gaseous hydrogen chloride and iodide distilled together with unchanged epichlorohydrin below 140°, and then at 1·5 mm. whereupon unchanged diphenylamine, b. p. 130—170°, and crude 3-hydroxy-1-phenyl-1 : 2 : 3 : 4-tetrahydroquinoline, b. p. 175—183°, were collected. The latter was purified by redistillation and solidified on storage. Recrystallisation from benzene–light petroleum gave a halogen-free product (7 g.), m. p. 78—79°; m. p. 79° is recorded in D.R.-P. 284,291. This compound (1 g.) and phenyl *iso*cyanate (1·4 g.) in dry benzene, when kept in a sealed tube for 3 days at 30°, gave a *carbanilate*, m. p. 127° (Found: N, 8·35. $C_{22}H_{20}O_2N_2$ requires N, 8·15%), needles from alcohol.

Reaction of Epichlorohydrin with p-*Toluidine*.—The use of aqueous alcohol as in the method of Cohn and Friedlaender (*loc. cit.*) gave 1-chloro-3-*p*-toluidinopropan-2-ol, leaflets (from alcohol), m. p. 81—82°. No distillate was obtained when this product was heated at 220°/0·8 mm.; there was a small sublimate of a basic hydrochloride. On cooling, the contents of the flask set to a hard resin which was only sparingly soluble in aqueous or organic solvents. When the chlorohydrin was stirred in benzene with 30% sodium hydroxide solution for 1 hour and the benzene was evaporated off at room temperature, a similar glassy resin was obtained, which has possible technical applications.

The micro-analyses were made by N. L. Lottkowitz. One of us (W. E. S.) acknowledges financial assistance from the Commonwealth Reconstruction Training Scheme.

ORGANIC CHEMISTRY LABORATORY,
UNIVERSITY OF MELBOURNE.

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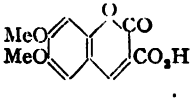
182. *The Chemistry of Fungi. Part IX. 3 : 4-Dihydrocoumarins.*

By F. M. Dean, Alexander Robertson, and W. B. Whalley.

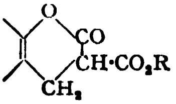
The preparation of typical 3 : 4-dihydrocoumarin-3-carboxylic acids and 3-acetyl-3 : 4-dihydrocoumarins by hydrogenation of the corresponding coumarin derivatives is described. From an examination of the properties of these products it has been concluded that *O*-dimethylcitromycin is not a derivative of 3 : 4-dihydrocoumarin as proposed in Part III (*loc. cit.*).

It is probable that the "diacetyl" derivative of 3 : 4-dihydrocoumarin described by Kaestner (*loc. cit.*) is 6-acetoacetyl-3 : 4-dihydrocoumarin.

From the evidence then available it was concluded in Part III (*J.*, 1949, 848) that citromycin and its dimethyl ether possessed a linear type of structure which could be envisaged as a cyclisation product of a 3 : 4-dihydrocoumarin derivative type (III; R = Ac). Further, the methylene group in the 4-position of the coumarin residue (III) was considered to be involved in the novel oxidation $:CH_2 \longrightarrow :CH(OH) \longrightarrow :CO$ effected with ozone and in the hydroxylation process with lead tetra-acetate, a view which appeared to receive support from studies on the oxidation of xanthens under similar conditions Part VIII (*J.*, 1949, 1567). The experiments described in the present communication were undertaken during our search for collateral evidence in support of the proposed structure for *O*-dimethylcitromycin and had three objectives: (*a*) to investigate the preparation of dihydrocoumarins of types (II) and (III; R = H) which could be employed as intermediates in the synthesis of (III; R = Ac) and hence of *O*-dimethylcitromycin; (*b*) to compare the 2 : 4-dinitrophenylhydrazone of (III; R = H) with the corresponding derivative, m. p. 282° (decomp.), of a product which was considered to be (III; R = H) (Part III, *loc. cit.*); and (*c*) to examine the behaviour of compounds of types (II) and (III; R = H) towards lead tetra-acetate and hydrolytic agents because compounds having structures (II) and (III; R = H) would provide a closer analogy with *O*-dimethylcitromycin than do the xanthens (Part VIII, *loc. cit.*).



(I.)



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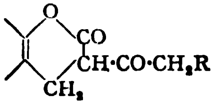


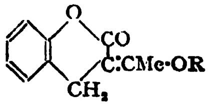
(III.)

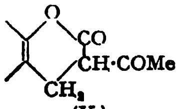
The preparation of 3 : 4-dihydrocoumarin-3-carboxylic acids containing a quinol nucleus by the hydrogenation of the corresponding coumarin-3-carboxylic acids has been extensively studied by Smith and his collaborators (see, *e.g.*, *J. Amer. Chem. Soc.*, 1936, **58**, 304) who have also described the preparation of 6-hydroxy- and 6-methoxy-3-acetyl-5 : 7 : 8-trimethyl-3 : 4-dihydrocoumarin by the hydrogenation of 6-hydroxy-3-acetyl-5 : 7 : 8-trimethylcoumarin and its methyl ether (*ibid.*, 1937, **59**, 667). In the present work similar methods have been employed.

The hydrogenation of coumarin-3-carboxylic acid in the form of its sodium salt with a palladium–charcoal catalyst gave a mixture of the expected 3 : *4-dihydrocoumarin-3-carboxylic acid* with its hydrated derivative, *2-hydroxybenzylmalonic acid*, which became the main product when 3 : 4-dihydrocoumarin-3-carboxylic acid, which separated initially on acidification of the filtered reaction mixture, was kept in contact with the mother-liquor. Methyl 2-hydroxybenzylmalonate was prepared by means of diazomethane and on distillation gave an almost quantitative yield of *methyl* 3 : *4-dihydrocoumarin-3-carboxylate* which was also formed by the hydrogenation of coumarin-3-carboxylic acid in methanol. The hydrogenation of 6 : *7-dimethoxycoumarin-3-carboxylic acid* (I) as its sodium salt furnished a mixture of 6 : 7-dimethoxy-3 : 4-dihydrocoumarin-3-carboxylic acid (II; R = H) and the corresponding benzylmalonic acid which on distillation in a vacuum gave rise to 6 : 7-dimethoxy-3 : 4-dihydrocoumarin. Treatment of the mixed acids with an excess of ethereal diazomethane gave the esters from which *methyl* 6 : *7-dimethoxy-*3 : *4-dihydrocoumarin-3-carboxylate* (II; R = Me) was isolated. When it was found that the acid chloride of 3 : 4-dihydrocoumarin-3-carboxylic acid could not be obtained by one or other of the standard methods, the preparation of other members of this series was abandoned.

Application of the hydrogenation process to 3-acetylcoumarin gave an excellent yield of *3-acetyl-*3 : *4-dihydrocoumarin* apparently as a keto–enol equilibrium mixture, in all probability (IV; R = H) and (V), from which the pure keto-form giving a negative ferric reaction was isolated. Acetylation of the mixture gave the *acetate* (IV; R = Ac) of the enolic compound which, as expected, did not react with ketonic reagents. The independent synthesis of 3-acetyl-

3 : 4-dihydrocoumarin in small yield by the interaction of 2-(*ethyl carbonato*)*benzylacetone* and ethyl carbonate in the presence of sodium served to confirm the structure of the compound. In contrast to the behaviour of the parent 3-acetylcoumarin the hydrogenation of 6 : 7-dimethoxy-3-acetylcoumarin was much slower and the main product was 6 : 7-*dimethoxy*-3-*ethylcoumarin* accompanied by only small amounts of the required 6 : 7-*dimethoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin* (III; R = H), the 2 : 4-dinitrophenylhydrazone, m. p. 228°, of which was not identical with the product, m. p. 282° (decomp.), obtained from *O*-dimethylcitromycin (Part III, *loc. cit.*); the yield of (III; R = H) was slightly increased when platinum–charcoal was employed as the catalyst in place of palladium–charcoal. Consequently we examined the hydrogenation of a number of analogous 3-acetylcoumarins under similar conditions.


(IV.)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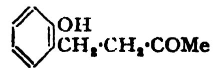
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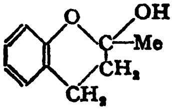
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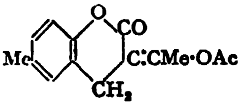
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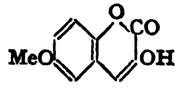

(IX.)

3-*Acetyl*-6-*methyl*- and 6-*methoxy*-3-*acetyl*-*coumarin* behaved normally, giving the respective 3 : 4-*dihydrocoumarins*. On the other hand 3-*acetyl*-7-*methyl*- and 7-*methoxy*-3-*acetyl*-*coumarin* gave only small yields of the 3 : 4-*dihydrocoumarins* which were separated from the main products of the reaction by taking advantage of the fact that 3-acetyl-3 : 4-dihydrocoumarins readily form chelated derivatives on treatment with aqueous copper acetate. From 3-acetyl-7-methylcoumarin the principal hydrogenation product was a compound which was readily differentiated from 7-*methyl*-3-*ethylcoumarin* and appeared to be 7-*methyl*-3-1′-*hydroxyethyl*-*coumarin*. With 7-methoxy-3-acetylcoumarin the main product was 7-*methoxy*-3-*ethylcoumarin*, whilst 7-hydroxy-3-acetylcoumarin gave only the corresponding 3-ethylcoumarin.

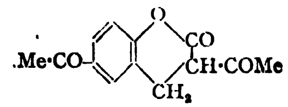
In their behaviour towards oxidising and hydrolytic agents the 3 : 4-dihydrocoumarin derivatives which have been examined showed a marked contrast to *O*-dimethylcitromycin under comparable conditions. 3 : 4-Dihydrocoumarin-3-carboxylic acid and its methyl ester, and 3-acetyl-3 : 4-dihydrocoumarin together with its 6-methyl and 6-methoxy-derivatives, readily underwent dehydrogenation with lead tetra-acetate, regenerating the parent coumarin derivatives which did not appear to be accompanied by detectable amounts of products oxygenated at the 4-position. In this connection it is of interest to note that 6-methoxy- and 6 : 7-dimethoxy-3-acetyl-3 : 4-dihydrocoumarin are readily dehydrogenated to the corresponding coumarins when solutions of the compounds are exposed to atmospheric oxygen, whilst in an alcoholic solution of 2 : 4-dinitrophenylhydrazine the 2 : 4-*dinitrophenylhydrazone* of 3-acetyl-3 : 4-dihydrocoumarin is oxidised to the 2 : 4-*dinitrophenylhydrazone* of 3-acetylcoumarin. The action of lead tetra-acetate clearly proceeds by the replacement of the active hydrogen atom in the 3-position of the 3-carboxy- or 3-acetyl-dihydrocoumarin by an acetoxy-group followed by the loss of acetic acid and the formation of the coumarin system. This reaction mechanism is in keeping with the failure of the reagent to dehydrogenate 3 : 4-dihydrocoumarin, its 6 : 7-dimethoxy-derivative, or the *acetate* (VIII) of the enolic form of 6-methyl-3-acetyl-3 : 4-dihydrocoumarin. On ozonolysis 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin furnished a mixture from which 3-*hydroxy*-6-*methoxycoumarin* and 2-hydroxy-4-methoxybenzaldehyde were isolated, but a search failed to reveal the presence of 4-hydroxy-6-methoxy-3-acetylcoumarin.

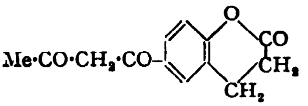
In their behaviour on hydrolysis with acidic and alkaline reagents 3-acetyl-3 : 4-dihydrocoumarins differ markedly from *O*-dimethylcitromycin. With these reagents the lactone ring of the dihydrocoumarin is opened and carbon dioxide is then eliminated, resulting in the formation of 2-hydroxybenzylacetones which, in the examples studied, have been isolated in the ketonic and cyclic forms represented by types (VI) and (VII) respectively. The alkali-insoluble cyclic forms readily give the 2 : 4-dinitrophenylhydrazones derived from the ketones.

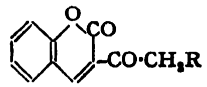
From our examination of the properties of 3 : 4-dihydrocoumarins it now seems reasonably certain that the citromycin molecule does not contain a 3 : 4-dihydrocoumarin residue as suggested in Part III (*loc. cit.*). Hydrolysis of citromycin or its dimethyl ether under a variety of conditions (Part III and unpublished work) has failed to yield products containing a

2-hydroxybenzylacetone nucleus. Further, the proposed formulæ for citromycin and its ether (Part III) implied that in the degradation of the ether to 2-hydroxy-4 : 5-dimethoxyacetophenone and -benzoic acid with alkali the methylene group in the 4-position of the 3 : 4-dihydrocoumarin residue was oxidised, whereas the authentic 3 : 4-dihydrocoumarin derivatives examined do not undergo degradation in this way.

In the course of exploratory experiments on the synthesis of 3-acetyl-3 : 4-dihydrocoumarins by alternate routes we examined the reaction reported by Kaestner ("Newer Methods of Preparative Organic Chemistry," 1948, New York, p. 296) by which 3 : 4-dihydrocoumarin is stated to be acetylated with the aid of boron trifluoride, giving the 3 : 6-diacetyl derivative (X). On the basis of this result it seemed reasonable to expect that 3 : 4-dihydrocoumarins substituted in the 6-position would give the 3-acetyl derivative (type III, R = H). This reaction failed, however, in the case of 6 : 7-dimethoxy-3 : 4-dihydrocoumarin, a result which led us to examine the diacetyl derivative of 3 : 4-dihydrocoumarin described by Kaestner who did not, however, record the melting point of the compound. Though our investigation is not yet complete, it appears that the compound is not 3 : 6-diacetyl-3 : 4-dihydrocoumarin (X), but, from the following considerations is, in all probability, 6-acetoacetyl-3 : 4-dihydrocoumarin (XI) :


(X.)


(XI.)


(XII.)

(*a*) Kaestner's compound gives a deep-red ferric reaction typical of compounds containing the group $\cdot CO\cdot CH_2\cdot CO\cdot$, whereas 3-acetyl-3 : 4-dihydrocoumarins invariably give a characteristic intense purple ferric reaction which we would not expect to be modified by the presence of an acetyl group in the 6-position.

(*b*) The compound is hydrolysed with 2N-aqueous sodium hydroxide to a product believed to be 6-acetyl-3 : 4-dihydrocoumarin (cf. Kaestner *loc. cit.*), whereas dihydrocoumarins *C*-acetylated in the 3-position invariably give a 2-hydroxybenzylacetone derivative.

(*c*) With lead tetra-acetate the compound reacts rapidly yielding an oil which retains the red ferric reaction—a property in keeping with the acetoxylation of a β-diketone, *i.e.*, $\cdot CO\cdot CH_2\cdot CO \longrightarrow \cdot CO\cdot CH(O\cdot COMe)\cdot CO\cdot$, whereas a dihydrocoumarin of the type (X) would be expected to undergo dehydrogenation yielding 3 : 6-diacetylcoumarin which would not give a ferric reaction.

(*d*) As far as we are aware β-ketonic esters cannot be prepared by the boron trifluoride–acetic anhydride method, and dihydrocoumarins substituted in the 6-position do not appear to form the corresponding 3-acetyl-3 : 4-dihydrocoumarins by this method. The latter compounds form comparatively stable complexes with boron trifluoride which do not react further and hence we were unable to prepare, by this route, 3-acetoacetyl-3 : 4-dihydrocoumarins cyclisation of which might be expected to give compounds having the type of structure proposed for *O*-dimethylcitromycin in Part III (*loc. cit.*). It would appear, therefore, that in Kaestner's preparation acetylation of dihydrocoumarin occurs first in the 6-position and, as the methyl of the *C*-acetyl group is more reactive than the α-methylene of an ester or lactone, further acetylation then takes place giving the 6-acetoacetyl derivative (XI) by way of the boron trifluoride complex. It is of interest to note that the acetylation of 3-acetylcoumarin (XII; R = H) by the same method gave 3-acetoacetylcoumarin (XII; R = Ac) which Trenknerowna (*Roczniki Chem.*, 1936, **16**, 6, 10) has synthesised by an independent route and which has a ferric reaction similar to Kaestner's compound.

EXPERIMENTAL.

3 : 4-*Dihydrocoumarin*-3-*carboxylic Acid.*—The sodium salt of coumarin-3-carboxylic acid in water (150 ml.) was prepared as a slurry from the acid (4 g.) and sodium hydrogen carbonate (2·1 g.) and subjected to hydrogenation with a palladium–charcoal catalyst (from 1 g. of charcoal and 0·4 g. of palladium chloride) and hydrogen at 62 lbs./sq. in. for 4 hours. On acidification with hydrochloric acid the filtered solution deposited during 10 minutes 3 : 4-*dihydrocoumarin*-3-*carboxylic acid* as a mass of fine needles (Found : C, 62·5; H, 4·5. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%) which had m. p. 142° after recrystallisation from water or ethyl acetate; the yield was somewhat variable, but in general about 2·5 g. were obtained from 4 g. of coumarin-3-carboxylic acid. This dihydro-acid is sparingly soluble in warm ligroin and readily soluble in alcohol or aqueous sodium hydrogen carbonate, and on being kept at 150—160° for 15 minutes decomposed with the evolution of carbon dioxide, giving a quantitative yield of 3 : 4-dihydrocoumarin, b. p. 178°/0·1 mm., which was identified by being converted into the

hydrazide, m. p. 166°, of melilotic acid (undepressed on admixture with an authentic specimen) (Pschorr and Einbeck, *Ber.*, 1905, **38**, 2070, gave m. p. 164—165°). Prepared by means of diazomethane, *methyl* 3 : *4-dihydrocoumarin-3-carboxylate* formed colourless prisms, m. p. 98—100°, from 85% alcohol, insoluble in aqueous sodium hydrogen carbonate and slowly soluble in 2N-aqueous sodium hydroxide (Found : C, 64·2; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

When the crude 3 : 4-dihydrocoumarin-3-carboxylic acid was left in contact with the acidified mother-liquor the solid dissolved, and on being kept for several weeks the solution gradually deposited *2-hydroxybenzylmalonic acid* in large colourless prisms, m. p. 142° (decomp.), readily soluble in aqueous sodium hydrogen carbonate [Found : C, 57·0; H, 4·9%; equiv. (by titration), 109·4. $C_{10}H_{10}O_5$ requires C, 57·2; H, 4·8%; equiv., 105]. A small quantity of this malonic acid was occasionally obtained from the solution left after the separation of 3 : 4-dihydrocoumarin-3-carboxylic acid. Although a mixture of this dibasic acid and 3 : 4-dihydrocoumarin-3-carboxylic acid did not show a depression in the melting point, it was clear that the two substances were not identical. Esterification of the dibasic acid with ethereal diazomethane yielded a liquid which, on distillation in a vacuum at 134—136°/0·5 mm., was completely converted into methyl 3 : 4-dihydrocoumarin-3-carboxylate, m. p. and mixed m. p. 98°, after purification.

Hydrogenation of coumarin-3-carboxylic acid (10 g.) in methanol (200 ml.) with a palladium–charcoal catalyst and hydrogen at 100 lbs./sq. in. gave an oil which, on distillation in a vacuum, partly crystallised. The solid, which slowly separated, was freed from adhering liquid by means of a porous tile and recrystallised from ethyl acetate–ligroin, giving methyl 3 : 4-dihydrocoumarin-3-carboxylate, m. p. and mixed m. p. 97—98° (Found : C, 63·9; H, 4·8%). This compound reacted with warm 50% hydrazine hydrate solution, giving the *2-hydroxybenzylmalonodihydrazide* which formed large colourless prisms, m. p. 236—240° (decomp.), from warm water (Found : C, 50·1; H, 5·8; N, 23·5. $C_{10}H_{14}O_3N_4$ requires C, 50·4; H, 5·9; N, 23·8%). The oil left after the separation of the crude methyl 3 : 4-dihydrocoumarin-3-carboxylate appeared to consist mainly of 3 : 4-dihydrocoumarin since it gave the hydrazide, m. p. and mixed m. p. 166°, of melilotic acid.

Dehydrogenation of 3 : *4-Dihydrocoumarin-3-carboxylic Acid.*—When powdered lead tetra-acetate (1 g.) was added to a solution of the acid (0·5 g.) in acetic acid (10 ml.) a white lead salt separated during 3 hours, and the mixture then had a negative starch–iodide reaction. Treatment of the solid with warm dilute nitric acid gave a yellow solution which on being cooled deposited coumarin-3-carboxylic acid in colourless prisms (0·18 g.), m. p. 202°, identical with an authentic specimen. When the acid was replaced by methyl 3 : 4-dihydrocoumarin-3-carboxylate (0·5 g.) in the foregoing experiment and the mixture kept for 24 hours and then diluted with water, methyl coumarin-3-carboxylate separated in colourless needles, m. p. 119—120°, after purification, identified by comparison with an authentic specimen.

6 : *7-Dimethoxycoumarin-3-carboxylic Acid* (I).—2-Hydroxy-4 : 5-dimethoxybenzaldehyde (3 g.) and sodium cyanoacetate (50 ml. of a solution prepared according to Phelps and Tillotson, *Amer. Journ. Science*, 1908, **26**, 275) were caused to react by means of sodium hydroxide (10 g.) in water (10 ml.) during 24 hours. Acidification of the reaction mixture with hydrochloric acid furnished a deep-yellow product which was heated under reflux with concentrated hydrochloric acid (20 ml.) and water (30 ml.) for 10 minutes, giving rise to the *coumarin-3-carboxylic acid.* Recrystallised from alcohol, this compound formed lemon-yellow needles (3 g.), m. p. 266° (decomp.), insoluble in water or ligroin and readily soluble in ethyl acetate, chloroform, or aqueous sodium hydrogen carbonate (Found : C, 57·5; H, 3·9. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). Prepared by means of ethereal diazomethane, the *methyl* ester separated from alcohol in yellow prisms, m. p. 212°, soluble in benzene or ethyl acetate (Found : C, 59·3; H, 4·6. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%). Alcoholic solutions of the acid or its ester exhibited an intense blue fluorescence.

Methyl 6 : *7-Dimethoxy-*3 : *4-dihydrocoumarin-3-carboxylate* (II; R = Me).—Hydrogenation of the foregoing coumarin-3-carboxylic acid (0·5 g.), dissolved in water (25 ml.) containing sodium hydrogen carbonate (0·17 g.), with 20% palladium–charcoal (1 g.) and hydrogen at 60 lbs./sq. in. for 4 hours gave a mixture consisting mainly of 2-hydroxy-4 : 5-dimethoxybenzylmalonic acid with small amounts of 6 : 7-dimethoxy-3 : 4-dihydrocoumarin-3-carboxylic acid which could not be conveniently separated. Recrystallised from water this product formed colourless needles (0·3—0·45 g.), m. p. 120° (decomp.), readily soluble in aqueous sodium hydrogen carbonate [Found : C, 50·5; H, 5·5%; equiv. (by titration) 135. Calc. for $C_{12}H_{12}O_6$: C, 57·1; H, 4·8%; equiv., 252. Calc. for $C_{12}H_{14}O_6,H_2O$: C, 50·0; H, 5·6%; equiv., 138]. On distillation at 155—160°/0·14 mm., the recrystallised product (1 g.) gave 6 : 7-dimethoxy-3 : 4-dihydrocoumarin (0·7 g.), m. p. 79—80° (Part II, *J.*, 1949, 565), and on treatment with an excess of ethereal diazomethane furnished an oil (1 g.) which, on being kept, deposited *methyl* 6 : *7-dimethoxy-*3 : *4-dihydrocoumarin-3-carboxylate* (II; R = Me) (0·1 g.), insoluble in cold dilute aqueous sodium hydroxide. Since it was readily soluble in alkali and on distillation at 190/0·1 mm. gave (II; R = Me) (0·7 g.), the residual oil appeared to be mainly methyl 2-hydroxy-4 : 5-dimethoxybenzylmalonate. Recrystallised from ethanol, the ester (II; R = Me) formed rectangular prisms, m. p. 151—152° (Found : C, 58·4; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%). Lead tetra-acetate (0·16 g.) in acetic acid (8 ml.) was added during 1 hour to a solution of methyl 6 : 7-dimethoxy-3 : 4-dihydrocoumarin-3-carboxylate (0·1 g.) in acetic acid (8 ml.), and 3 hours later the mixture was diluted with water (50 ml.), giving methyl 6 : 7-dimethoxycoumarin-3-carboxylate which slowly separated in long lemon-yellow needles, m. p. 212°, identical with an authentic specimen.

*3-Acetyl-*3 : *4-dihydrocoumarin.*—(*a*) 3-Acetylcoumarin (Knoevenagel, *Ber.*, 1898, **31**, 732) formed a 2 : *4-dinitrophenylhydrazone* which separated from acetic acid in orange prisms, m. p. 257—258° (decomp.) (Found : C, 55·2; H, 3·5; N, 14·9. $C_{17}H_{12}O_6N_4$ requires C, 55·4; H, 3·3; N, 15·3%).

A suspension of 3-acetylcoumarin (5 g.) in methanol (200 ml.) was agitated with palladium–charcoal (from 1 g. of charcoal and 0·1 g. of palladium chloride) and hydrogen at 60 lbs./sq. in. at room temperature for 1 hour and the filtered reaction mixture evaporated in a vacuum at 40°, leaving a colourless residue (4·8 g.), m. p. ~58°; traces of mineral acid in the catalyst or evaporation at higher temperatures caused decomposition of the product. Recrystallisation of the residual solid from aqueous methanol or benzene–ligroin gave 3-*acetyl*-3 : 4-*dihydrocoumarin* in colourless elongated plates, m. p. 62°, giving a deep-purple ferric reaction in alcohol (Found : C, 69·8; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). This compound is insoluble in aqueous sodium hydrogen carbonate, sparingly soluble in cold ligroin, and readily soluble in benzene, alcohol, chloroform, or 1% aqueous sodium hydroxide. The *oxime* separated from aqueous alcohol in colourless prisms, m. p. 174° (decomp.) after becoming reddish-brown at 160—170°, which are readily soluble in dilute aqueous sodium hydroxide (Found : C, 65·0; H, 5·4; N, 6·6. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%). Crystallised from alcohol, the *semicarbazone* was obtained in colourless prisms, m. p. 188°, which exhibited a royal-blue ferric reaction in alcohol and were instantly soluble in cold 2N-aqueous sodium hydroxide (Found : C, 58·2; H, 5·5; N, 17·3. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow needles, m. p. 174° (Found : C, 55·3; H, 3·7; N, 14·9. $C_{17}H_{14}O_6N_4$ requires C, 55·1; H, 3·8; N, 15·1%). When the crude hydrazone was allowed to remain in contact with the excess of 2 : 4-dinitrophenylhydrazine solution for about a week, its colour changed to deep orange. Recrystallised from ethyl acetate the product then gave the 2 : 4-dinitrophenylhydrazone of 3-acetylcoumarin in orange prisms, m. p. 258° (decomp.), identified by comparison with an authentic specimen. Addition of aqueous copper acetate to an alcoholic solution of 3-acetyl-3 : 4-dihydrocoumarin gave a precipitate of the insoluble copper derivative from which the dihydrocoumarin was regenerated by treatment with cold dilute mineral acid and ether, followed by evaporation of the dried ethereal liquor.

A mixture of 3-acetyl-3 : 4-dihydrocoumarin (0·5 g.), acetic anhydride (2 ml.), and pyridine (2 ml.) was warmed on the steam-bath for 10 minutes, kept for 24 hours, and poured into an excess of dilute hydrochloric acid. The resulting oily O-*acetyl* derivative solidified in contact with a little alcohol and then crystallised from aqueous alcohol in slender prisms (0·4 g.), m. p. 65—66°, insoluble in cold dilute aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 67·5; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). Mixed with the parent compound the acetyl derivative had m. p. 38—50°.

During numerous hydrogenation experiments with 3-acetyl-3 : 4-dihydrocoumarin it was found that the m. p. of the product varies between 58° and 63° but the product which separated from alcoholic solvents usually had m. p. 62° and, when fused, allowed to solidify, and then re-heated, this material melted again at 62°. After being kept for several months a sample, which originally had m. p. 62°, melted at 66°. On one occasion the spontaneous evaporation of a dilute benzene–light petroleum (b. p. 60—80°) solution of a sample, m. p. 62°, which had been crystallised several times from dilute methanol, gave large prisms, m. p. 67°, which appeared to be the pure keto-form (V), since it had a negative ferric reaction in alcohol and instantaneously gave the 2 : 4-dinitrophenylhydrazone, m. p. 172°, identical with that obtained from the material, m. p. 62°. When a solution of this apparently pure keto-compound in alcohol was warmed, cooled, and treated with a drop of aqueous ferric chloride it gave the intense purple colour, indicating the presence of the enolic form in the solution. Repeated fusion, followed by cooling, of the pure keto-compound gave the product, m. p. 62°. A mixture of the latter and the keto-compound, m. p. 67°, had m. p. 63—66° which changed to 62° on repeated fusion.

(*b*) Ethyl chloroformate (2·0 g.) was added drop-wise to a vigorously agitated solution of 2-hydroxybenzylacetone (Harries, *Ber.*, 1891, **24**, 3180) (2 g.) in a slight excess of N-aqueous sodium hydroxide, and one hour later the resulting 2-(*ethyl carbonato*)*benzylacetone* was isolated with ether and purified by distillation, being obtained as a colourless oil (1·7 g.), b. p. 125—128°/0·2 mm., readily soluble in the usual organic solvents except ligroin (Found : C, 66·9; H, 6·9. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·9%). A mixture of this ketone (1·7 g.), pulverised sodium (1 g.), and ethyl carbonate (10 g.) was kept at 80° for 3 hours and the resulting flocculent precipitate was collected, washed with ether, dried, and dissolved in water covered with a layer of ether. This mixture was saturated with carbon dioxide, the ethereal layer was separated and evaporated, a solution of the oily residue in a little alcohol was treated with saturated aqueous copper acetate, and the resulting green precipitate (80 mg.) was washed with water, alcohol, and ether and decomposed with 5% sulphuric acid in the presence of ether, giving 3-acetyl-3 : 4-dihydrocoumarin (50 mg.) which formed colourless prisms, m. p. 62—63°, from light petroleum (b. p. 60—80°), identical with a specimen prepared by method (*a*), and gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 170°. Left in contact with 2 : 4-dinitrophenylhydrazine solution the latter derivative gave rise to the 2 : 4-dinitrophenylhydrazone of 3-acetylcoumarin, m. p. 257—258° (decomp.).

When the pale yellow solution of 3-acetyl-3 : 4-dihydrocoumarin (0·5 g.) in N-aqueous sodium hydroxide (6 ml.) was heated on the steam-bath for ½ hour a pale yellow oil (negative ferric reaction) separated and was isolated from the cooled mixture with ether. Acidification of the residual alkaline liquor, followed by extraction with ether, gave a small amount of a phenolic product. These compounds, which are respectively 2-hydroxy-2-methylchroman and its isomeride 2-hydroxybenzylacetone (Harries, *Ber.*, 1891, **24**, 3180), have a characteristic pleasant odour and give the same 2 : 4-*dinitrophenylhydrazone*, which forms bright yellow prisms, m. p. 152°, identified by comparison with an authentic specimen (Found : C, 55·3; H, 4·5; N, 16·3. $C_{16}H_{16}O_5N_4$ requires C, 55·8; H, 4·7; N, 16·3%).

When lead tetra-acetate (1·1 g.) was added to a solution of 3-acetyl-3 : 4-dihydrocoumarin (0·5 g.) in acetic acid (15 ml.) the mixture became slightly warm and the lead salt gradually dissolved. 2 Hours later the resulting pale yellow solution gave a negative test for quadrivalent lead and, on the addition of an excess of water, deposited 3-acetylcoumarin as an oil which quickly solidified and then crystallised from dilute methanol in pale yellow prisms, m. p. 123°, undepressed on admixture with an authentic specimen. The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 258° (decomp.).

3-*Acetyl*-6-*methyl*-3 : 4-*dihydrocoumarin*.—Prepared by the hydrogenation of 3-acetyl-6-methylcoumarin (Chuit and Bolsing, *Bull. Soc. chim.*, 1915, **35**, 89) (2 g.), 3-*acetyl*-6-*methyl*-3 : 4-*dihydrocoumarin* (1·9 g.) separated from ligroin and then dilute alcohol in colourless prisms, m. p. 71—73°, soluble in hot water, alcohol, or ethyl acetate, and giving an intense purple ferric reaction in alcohol (Found : C, 71·1; H, 5·7. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* formed orange-yellow prisms, m. p. 195—196°, from ethyl acetate (Found : C, 56·0; H, 4·1; N, 14·3. $C_{18}H_{16}O_6N_4$ requires C, 56·3; H, 4·2; N, 14·6%). The *semicarbazone* separated from alcohol and then methanol in colourless prisms or needles, m. p. 265° (decomp.), readily soluble in 2N-aqueous sodium hydroxide and giving a royal-blue ferric reaction in alcohol (Found : C, 59·9; H, 6·0; N, 16·4. $C_{13}H_{15}O_3N_3$ requires C, 59·7; H, 5·8; N, 16·1%).

Acetylation of 3-acetyl-6-methyl-3 : 4-dihydrocoumarin (2 g.) with acetic anhydride (6 ml.) and pyridine (3 ml.) at room temperature for 16 hours gave an oily solid which, after having been drained on a porous tile, was crystallised from dilute alcohol and then dilute methanol, giving the *acetate* (VIII) of the enolic form of the coumarin in colourless shining plates, m. p. 125° (Found : C, 68·1; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). This compound, which is soluble in benzene and in hot ligroin, gives a negative ferric reaction in alcohol and does not react with 2 : 4-dinitrophenylhydrazine.

A solution of 3-acetyl-6-methyl-3 : 4-dihydrocoumarin (1 g.) in 2N-sodium hydroxide (10 ml.) was heated on the steam-bath for ½ hour, cooled, and extracted with ether. Evaporation of the dried ethereal extract left a neutral oil, whilst saturation of the residual alkaline liquor with carbon dioxide followed by extraction with ether gave a phenolic oil These phenolic and neutral products, which had similar odours and became purple on being heated, appear to be 2-hydroxy-4-methylbenzylacetone and its cyclic form, 2-hydroxy-2 : 6-dimethylchroman, respectively, since they give rise to the same 2 : *4-dinitrophenylhydrazone*, forming orange plates, m. p. 165—166°, from dilute alcohol, readily soluble in 1% aqueous sodium hydroxide (Found : C, 57·4; H, 5·4. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·0%).

Oxidation of 3-acetyl-6-methyl-3 : 4-dihydrocoumarin (1 g.) with lead tetra-acetate (2·1 g.) in acetic acid (15 ml.) at room temperature for 2 hours gave 3-acetyl-6-methylcoumarin (0·85 g.) which formed pale yellow plates, m. p. 131°, from methanol, identical with an authentic specimen. The 2 : *4-dinitrophenylhydrazone* separated from ethyl acetate in orange prisms, m. p. 256—258°, undepressed on admixture with an authentic specimen (Found : N, 14·9. $C_{18}H_{14}O_6N_4$ requires N, 14·7%).

6-*Methoxy*-3-*acetylcoumarin*.—A few drops of piperidine were added to a mixture of 2-hydroxy-4-methoxybenzaldehyde (Tiemann and Muller, *Ber.*, 1881, **14**, 1990) (10 g.) and ethyl acetoacetate (10 ml.), and the reaction was completed by heating the deep-yellow solution on the steam-bath for 10 minutes. On being cooled the reaction mixture deposited 6-*methoxy*-3-*acetylcoumarin* as a yellow crystalline mass which, after the addition of alcohol (10 ml.), was collected and purified from this solvent, forming brilliant yellow plates (12 g.), m. p. 182—183° (Found : C, 65·9; H, 4·8. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6%). The 2 : *4-dinitrophenylhydrazone* separated from ethyl acetate in diamond-shaped plates, m. p. 242—243° (Found : N, 14·3. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

6-*Methoxy*-3-*acetyl*-3 : *4-dihydrocoumarin*.—Hydrogenation of the foregoing coumarin (1 g.) in methanol (200 ml.) with palladium–charcoal and hydrogen at 60 lbs./sq. in., followed by evaporation of the filtered reaction mixture in a vacuum at 40°, gave a gummy solid (0·95 g.) which was purified by repeated crystallisation from alcohol and then light petroleum (b. p. 60—80°), furnishing 6-*methoxy*-3-*acetyl*-3 : *4-dihydrocoumarin* in pale yellow prisms, m. p. 82—84°. It was observed during the purification from alcohol that each time the compound was dissolved in the solvent a small amount of a highly insoluble yellow product was formed which was found to be 6-methoxy-3-acetylcoumarin arising by the atmospheric oxidation of the 3 : 4-dihydrocoumarin in alcoholic solution. Purified from alcohol, the 6-methoxy-3-acetylcoumarin formed yellow needles, m. p. and mixed m. p. 182—183°, and gave the 2 : 4-dinitrophenylhydrazone, m. p. 242°. When the isolation and purification of the hydrogenation product were carried out in an atmosphere of nitrogen, 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin was obtained in colourless prisms, m. p. 82—84°, giving a purple ferric reaction in alcohol (Found : C, 65·6; H, 5·3. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). On exposure to air alcoholic solutions of this compound absorb oxygen and give a quantitative yield of 6-methoxy-3-acetylcoumarin. The 2 : *4-dinitrophenylhydrazone* separated from ethyl acetate in light-orange spearheads, m. p. 184—185° (Found : C, 54·0; H, 4·0; N, 14·0. $C_{18}H_{16}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%). The *semicarbazone* formed large flat prisms, m. p. 188—189°, from alcohol, readily soluble in 2N-aqueous sodium hydroxide and giving a royal-blue colour with alcoholic ferric chloride, unaffected on dilution with water (Found : C, 56·3; H, 5·4; N, 14·8. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·4; N, 15·2%).

Hydrolysis of 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin (1 g.) with 0·5N-aqueous sodium hydroxide (20 ml.) on the steam-bath for 30 minutes gave the neutral 2-hydroxy-6-methoxy-2-methylchroman and the phenolic 2-hydroxy-5-methoxybenzylacetone, each of which furnished the 2 : *4-dinitrophenylhydrazone* of 2-hydroxy-5-methoxybenzylacetone, forming scarlet rectangular prisms, m. p. 156°, from dilute alcohol (Found : C, 54·6; H, 5·0; N, 14·9. $C_{17}H_{18}O_6N_4$ requires C, 54·5; H, 4·8; N, 15·0%). When the coumarin was heated under reflux with N-alcoholic hydrochloric acid for 45 minutes the same mixed product was obtained, giving the 2 : 4-dinitrophenylhydrazone, m. p. 156°.

Oxidation of 6-*Methoxy*-3-*acetyl*-3 : *4-dihydrocoumarin*.—(*a*) Dehydrogenation of 6-methoxy-3-acetyl-3 : 4-dihydrocoumarin (0·5 g.) in acetic acid (10 ml.) with lead tetra-acetate (1 g.) proceeded rapidly, giving 6-methoxy-3-acetylcoumarin, m. p. and mixed m. p. 182°, which formed the 2 : 4-dinitrophenylhydrazone, m. p. 242—243°.

(*b*) A slow stream of ozone and oxygen was led into a solution of the dihydrocoumarin (1 g.) in chloroform (75 ml.) maintained at 0° for 75 minutes, the solvent was removed in a vacuum, and the residue treated with water. Next day the water was decanted and on treatment with a little ether the residual oil gave crystalline 3-hydroxy-6-methoxycoumarin which separated from ethyl acetate in pale yellow prisms, m. p. 208—209°, giving an intense deep green ferric reaction in alcohol and identified by comparison with an authentic specimen. The ethereal filtrate from the crude 3-hydroxy-6-methoxycoumarin contained 2-hydroxy-5-methoxybenzaldehyde which was identified by conversion into the 2 : *4-dinitrophenylhydrazone*, m. p. 263°, undepressed on admixture with an authentic sample (Found : N, 17·1. $C_{14}H_{12}O_6N_4$ requires N, 16·9%).

3-*Hydroxy*-6-*methoxycoumarin* (IX).—A mixture of 2-hydroxy-5-methoxybenzaldehyde (2 g.), aceturic acid (2·5 g.), acetic acid (3 ml.), acetic anhydride (10 ml.), and sodium acetate (1·6 g.) was heated on the steam-bath for 2 hours. The colourless crystalline product which separated from the cooled reaction mixture was removed, the residual liquor was diluted with water, and the yellow precipitate collected, washed with a little alcohol and then with ether to remove traces of resinous material. The crude azlactone (0·5 g.) was then boiled with 2N-hydrochloric acid (20 ml.) for 4 hours and the resulting 3-*hydroxy*-6-*methoxycoumarin* (0·3 g.) was isolated by filtration from the cooled reaction mixture. Crystallised from alcohol (charcoal) and then from ethyl acetate, the compound formed pale fawn-coloured prisms, m. p. 208—210°, readily soluble in 1% aqueous sodium hydroxide and giving a characteristic deep-green ferric reaction (Found: C, 62·6; H, 4·3. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%).

Hydrogenation of 3-Acetyl-7-methylcoumarin.—This coumarin (Chuit and Bolsing, *Bull. Soc. chim.*, 1915, **35**, 84) formed a 2 : 4-*dinitrophenylhydrazone*, separating from acetic acid or ethyl acetate in masses of slender yellow needles, m. p. 225—226° (Found: N, 14·6. $C_{18}H_{14}O_6N_4$ requires N, 14·7%).

When the hydrogenation of the coumarin (2 g.) was effected by the procedure employed in the case of 6-methyl-3-acetylcoumarin the colourless product left on evaporation of the filtered reaction mixture had m. p. 80—90°, and gave a purple ferric reaction in alcohol. Crystallisation of this material several times alternately from aqueous methanol and benzene–ligroin and then from alcohol and benzene gave a *substance* in colourless prisms (1 g.), m. p. 129·5—130·5°, which was sparingly soluble in benzene and did not react with 2 : 4-dinitrophenylhydrazine or give a ferric reaction (Found: C, 70·8; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). This product dissolved slowly in hot 2N-aqueous sodium hydroxide and on acidification with dilute hydrochloric acid the original material, m. p. 128°, was obtained. It was not identical either with 7-methylcoumarin, m. p. 128° (the mixture of two compounds melted at 88—110°), or with 3-ethyl-7-methylcoumarin.

Treatment of the alcoholic mother-liquors left from the purification of the foregoing product with an excess of saturated copper acetate gave an amorphous green precipitate (1·2 g. from 3 g. of 3-acetyl-7-methylcoumarin) which, after having been washed with water, methanol, and then with ether, was decomposed with a mixture of 5% sulphuric acid and ether. Evaporation of the ethereal liquor gave 3-*acetyl*-7-*methyl*-3 : 4-*dihydrocoumarin* which formed colourless platelets (0·56 g.), m. p. 95—97°, from dilute alcohol, readily soluble in the usual organic solvents except ligroin and giving a purple ferric reaction in alcohol (Found: C, 70·9; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow needles, m. p. 190—192° (Found: C, 56·1; H, 4·2; N, 14·3. $C_{18}H_{16}O_6N_4$ requires C, 56·4; H, 4·2; N, 14·6%).

7-*Methyl*-3-*ethylcoumarin* was prepared by the butyrylation of 2-hydroxy-4-methylbenzaldehyde (3 g.) with butyric anhydride (5 g.) and sodium butyrate (5 g.) at 170° for 5hours and subsequent treatment of the reaction mixture with water. Crystallised from light petroleum (b. p. 60—80°), the coumarin (1·6 g.) formed colourless flat needles, m. p. 63—64°, soluble in alcohol or ethyl acetate (Found: C, 76·6; H, 6·6. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

7-Methoxy-3-acetylcoumarin.—Condensation of 4-*O*-methylresorcylaldehyde (6 g.) and ethyl acetoacetate (6 ml.) by means of a little piperidine gave rise to 7-*methoxy*-3-*acetylcoumarin* which separated from ethyl acetate in pale yellow prisms (8 g.), m. p. 173—174° (Found: C, 66·0; H, 4·5. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%), showing in alcohol an intense blue fluorescence. Prepared by the pyridine method, the *oxime* formed almost colourless prisms, m. p. 217°, from alcohol and then ethyl acetate (Found: N, 5·6. $C_{12}H_{11}O_4N$ requires N, 6·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in tiny scarlet rhombs, m. p. 257—258° (decomp.) (Found: N, 14·1. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

Hydrogenation of 7-Methoxy-3-acetylcoumarin.—This coumarin (2 g.) was hydrogenated in methanol (300 ml.) with hydrogen at 60 lbs./sq. in. and palladium–charcoal (from 1 g. of charcoal and 0·3 g. of palladium chloride) during 2½ hours at room temperature. The colourless, filtered reaction mixture, which gave only a comparatively faint purple ferric reaction and only traces of a precipitate with 2 : 4-dinitrophenylhydrazine solution, was concentrated in a vacuum at below 50°, giving a crystalline solid (0·5 g.) which consisted mainly of 7-*methoxy*-3-*ethylcoumarin*. Recrystallised from methanol and then ethyl acetate–ligroin, this compound formed colourless prisms, m. p. 98—100°, (Found: C, 70·1; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%) undepressed on admixture with an authentic sample (cf. below).

Concentration of the liquor left after the separation of the crude 7-methoxy-3-ethylcoumarin furnished a solution which gave a purple ferric reaction and on treatment with an excess of aqueous copper acetate gave the copper derivative of 7-*methoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin*; the amount of this derivative obtained was variable, the maximum being 0·2 g. from 2 g. of 7-methoxy-3-acetylcoumarin. Decomposition of the crude copper compound was effected with 5% sulphuric acid (20 ml.) containing ether (20 ml.) (agitate) during 2 hours at room temperature, and the ethereal solution was separated, washed with aqueous sodium hydrogen carbonate, dried, and evaporated, leaving the dihydrocoumarin which formed colourless, elongated, flat prisms, m. p. 82·5—84·5°, from light petroleum (b. p. 60—80°) and gave an intense purple ferric reaction in alcohol (Found: C, 65·8; H, 5·4. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

An authentic specimen of 7-methoxy-3-ethylcoumarin was prepared by heating a mixture of 4-*O*-methylresorcylaldehyde (3 g.), sodium butyrate (6 g.), and butyric anhydride (6 g.) at 160° for 4 hours. The reaction mixture was boiled with water to decompose the excess of anhydride, cooled, and extracted with ether. Evaporation of the ethereal solution, which had been washed successively with N-aqueous sodium hydroxide and water and then dried, left a brown oil which partly solidified and on purification from methanol and then ethyl acetate–ligroin, gave 7-methoxy-3-ethylcoumarin in colourless prisms, m. p. 99—100°, soluble in alcohol, ethyl acetate, or chloroform (Found: C, 70·7; H, 6·0%).

Hydrogenation of 7-Hydroxy-3-acetylcoumarin.—This coumarin, m. p. 236°, was prepared by the condensation of β-resorcylaldehyde and ethyl acetate with a little pyridine (compare Weiss and Merksammer, *Monatsh.*, 1928, **50**, 115) and gave a 2 : 4-*dinitrophenylhydrazone*, forming scarlet needles, m. p. 302—303° (decomp.), from ethyl acetate (Found: N, 14·7. $C_{17}H_{12}O_7N_4$ requires N, 14·6%).

Hydrogenation of the coumarin (1 g.) by the procedure employed for its 7-methyl ether gave a tan-coloured crude product (1 g.), m. p. 70—100°, giving a faint violet ferric reaction in alcohol and forming, in dilute aqueous sodium hydroxide, a solution which had a brilliant blue fluorescence. A solution of this solid in a little hot alcohol was warmed with saturated aqueous sodium hydrogen sulphite (3 ml.) on the steam-bath for 15 minutes and on cooling the mixture deposited crystalline material which was collected and again treated with warm alcohol and aqueous sodium hydrogen sulphite, finally giving 7-hydroxy-3-ethylcoumarin as a monohydrate in colourless shining needles, m. p. 128—129°, giving a negative ferric reaction (Fichter and Goldhaber, *Ber.*, 1904, **37**, 2382, record m. p. 123—124°) (Found : C, 63·2; H, 5·7. Calc. for $C_{11}H_{10}O_3,H_2O$: C, 63·5; H, 5·8%). Methylation of this compound by the potassium carbonate–methyl iodide method during 2 hours gave 7-methoxy-3-ethylcoumarin which separated from aqueous methanol in colourless prisms, m. p. 98—100°, undepressed on admixture with an authentic specimen.

Hydrogenation of 6 : 7-*Dimethoxy*-3-*acetylcoumarin.*—The *oxime* of this coumarin (Part II, *loc. cit.*) formed colourless slender needles, m. p. 218°, from alcohol (Found : N, 5·3. $C_{13}H_{13}O_5N$ requires N, 5·3%). The 2 : 4-dinitrophenylhydrazone had m. p. 282—283° (decomp.) and not 280° (decomp.) as given in Part II (*loc. cit.*).

Hydrogenation of the coumarin (2 g.) in methanol with palladium–charcoal and hydrogen at 60 lbs./sq. in. during 5—6 hours gave, after filtration, a colourless solution which gave a faint ferric reaction and became yellow on exposure to air.

Evaporation of the solution in an atmosphere of nitrogen, followed by extraction of the residue with a little hot methanol, left unchanged 6 : 7-dimethoxy-3-acetylcoumarin, m. p. 228°. On cooling, the methanolic extract deposited 6 : 7-*dimethoxy*-3-*ethylcoumarin* in pale yellow needles, m. p. 108—109°, identical with an authentic specimen (Found : C, 66·7; H, 5·9. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The latter specimen was prepared by the butyrylation of 2-hydroxy-4 : 5-dimethoxybenzaldehyde with butyric anhydride and sodium butyrate at 170° for 6 hours and on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) was obtained in large prisms, m. p. 108—109° (Found : C, 66·6; H, 5·9%).

When a platinum–charcoal catalyst was employed in the hydrogenation and the product was subjected to prolonged fractional crystallisation in an atmosphere of nitrogen there was obtained, in addition to 6 : 7-dimethoxy-3-ethylcoumarin, a small amount of 6 : 7-*dimethoxy*-3-*acetyl*-3 : 4-*dihydrocoumarin* (III; R = H). By treatment of several batches of filtered hydrogenation-liquor with an excess of aqueous copper acetate a small amount of the copper derivative of the latter coumarin was obtained which was washed with warm alcohol, chloroform, and ether and decomposed with dilute sulphuric acid and ether in the usual manner giving 6 : 7-dimethoxy-3-acetyl-3 : 4-dihydrocoumarin, forming colourless prisms, m. p. 164—166°, from alcohol (Found : C, 62·2; H, 5·6. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). This compound was soluble in chloroform, ethyl acetate, benzene, or warm 1% aqueous sodium hydroxide and gave a purple ferric reaction in alcohol. Formed in the usual manner, the 2 : 4-dinitrophenylhydrazone was obtained as an orange yellow precipitate, m. p. 228°, which could not be satisfactorily recrystallised.

6-*Acetoacetyl*-3 : 4-*dihydrocoumarin* (XI).—A solution of 3 : 4-dihydrocoumarin (3 g.) in acetic anhydride (8 ml.) at 0° was saturated with boron trifluoride (from 22 g. of potassium fluoroborate) and treated with ice-water 24 hours later. The boron fluoride complex of the diketone then slowly separated from the reaction mixture in pale yellow needles (2·3 g.), m. p. 120°. Decomposition of this (1 g.) with boiling water (3 ml.) containing hydrated sodium acetate (10 g.) during 10 minutes gave 6-acetoacetyl-3 : 4-dihydrocoumarin, which was isolated from the cooled mixture with ether, purified by way of its copper derivative, and crystallised from ligroin or dilute alcohol, forming a hydrate in small colourless prisms (0·7 g.) giving a deep-red ferric reaction (Found : C, 62·3; H, 5·8. Calc. for $C_{13}H_{12}O_4,H_2O$: C, 62·4; H, 5·6%) (cf. Kaestner, *loc. cit.*).

3-*Acetoacetylcoumarin* (XII; R = Ac).—A mixture of 3-acetylcoumarin (3 g.), acetic acid (10 ml.), and acetic anhydride (6 ml.) was saturated at room temperature with boron trifluoride, and ½ hour later the red viscous liquid was poured into water (50 ml.). Extraction of the washed, flocculent, orange-yellow product (3·7 g.) with alcohol removed viscous reddish impurities and left the boron fluoride complex of 3-acetoacetylcoumarin as a mass of orange crystals (2·3 g.), which, on recrystallisation from acetic acid formed yellow plates, m. p. 268°, sparingly soluble in organic solvents and giving a green flame test. On being heated on the steam-bath with acetic acid (50 ml.) and hydrated sodium acetate (2 g.) this compound (2·4 g.) slowly dissolved; after ½ hour water was added until the solution became faintly opalescent; 3-acetoacetylcoumarin (XII; R = Ac) separated from the cooled mixture in pale yellow prisms (1·5 g.), and, on recrystallisation from alcohol and then acetic acid, had m. p. 152—153° (Found : C, 67·5; H, 4·4. Calc. for $C_{13}H_{10}O_4$: C, 67·8; H, 4·4%). This compound, which gave a red ferric reaction in alcohol, was readily soluble in 2N-aqueous sodium hydroxide and insoluble in aqueous sodium carbonate. The 2 : 4-dinitrophenylhydrazone and the oxime were obtained as amorphous solids which could not be induced to crystallise (cf. Trenknerowna, *Roczniki Chem.*, 1936, **16**, 6, 10, who states that the compound gives a blood-red ferric reaction and forms cream-yellow needles or blunt prisms, m. p. 143—144°).

Hydrogenation of this coumarin by the procedure employed for 3-acetylcoumarin gave a gummy product which was resolved by means of ether into unchanged 3-acetoacetylcoumarin and a small amount of a *substance* which formed elongated needle-shaped plates, m. p. 177—178°, from alcohol, giving a negative ferric reaction (Found : C, 67·1; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). It did not appear to react with 2 : 4-dinitrophenylhydrazine.

UNIVERSITY OF LIVERPOOL.

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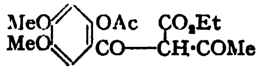
183. *The Chemistry of Fungi. Part X. The Synthesis of 4-Hydroxy-3-acetylcoumarins.*

By G. G. Badcock, F. M. Dean, Alexander Robertson, and W. B. Whalley.

Methods for the synthesis of 4-hydroxy-3-acetylcoumarins have been re-investigated and the novel synthetical procedures described in Part II (*loc. cit.*) have been further developed. It has been found that 4-hydroxycoumarins unsubstituted in the 3-position can be acetylated readily with acetic anhydride and boron trifluoride in acetic acid to give 4-hydroxy-3-acetylcoumarins, thus affording an unequivocal route to these interesting compounds. By this reaction the synthetic compound (Part II, *J.*, 1949, 562), m. p. 250°, has now been shown conclusively to be 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin. The hydrolysis product, m. p. 208°, from *O*-dimethylcitromycinone (Part III, *J.*, 1949, 848) has been found to have formula (XIV) and arises by the hydration of the parent compound (XV) which it regenerates on treatment with concentrated sulphuric acid.

In the course of degradative experiments on *O*-dimethylcitromycinone (Part III, *J.*, 1949, 848) there was isolated a faintly acidic substance, m. p. 208°, which was regarded as 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III) because it appeared to have the empirical formula $C_{11}H_6O_4(OMe)_2$, readily formed a 2 : 4-dinitrophenylhydrazone, and gave the requisite products on hydrolytic decomposition with alkalis. Unexpectedly, when the method of Anschütz (*Annalen*, 1906, **346**, 286) and the two novel procedures, *viz.*, the carbonyl chloride and the ethyl carbonate methods described in Part II (*J.*, 1949, 562), were applied to the synthesis of the coumarin (III) a product *P*, m. p. 250°, was invariably obtained which appeared not to react with 2 : 4-dinitrophenylhydrazine and was clearly not identical with the natural degradation product, m. p. 208°. From an examination of its properties and hydrolytic products, and in view of its apparent isomerism with the degradation product, m. p. 208°, the substance *P* was considered to be 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (X; R = H). At the same time it was noted that the production of small amounts of 4-hydroxy-6 : 7-dimethoxycoumarin (IV) by the hydrolysis of *P* with alkalis was more in keeping with the 4-hydroxy-3-acetylcoumarin structure (III), but a plausible mechanism advanced for the derivation of 4-hydroxy-6 : 7-dimethoxycoumarin from (X; R = H) seemed to reconcile the apparent anomaly. Because of the possible ambiguity regarding the nature of the products obtained by the methods hitherto employed for the synthesis of 4-hydroxy-3-acetylcoumarins and since the substance, m. p. 208°, was regarded as an important hydrolytic product in the degradation series derived from *O*-dimethylcitromycinone, it seemed desirable to re-investigate the synthetical procedures and to examine the properties of 4-hydroxy-3-acetylcoumarins in some detail.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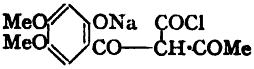
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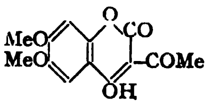
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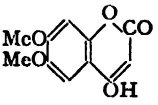
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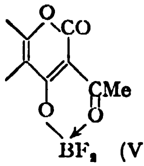
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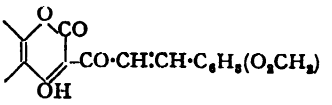
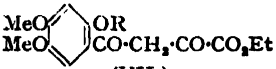
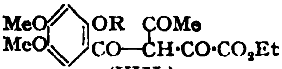

(VI.)

In our hands the procedure for the synthesis of 4-hydroxy-3-acetylcoumarins described by Anschütz (*loc. cit.*) gave somewhat uncertain results and a modified technique is now described whereby consistent yields of the required coumarins have been obtained. Of the novel alternative methods proposed in Part II (*loc. cit.*) the *o*-hydroxybenzoylacetone–ethyl carbonate method in the case of *2-hydroxy-* and *2-hydroxy-5-methyl-benzoylacetone* failed to yield the expected 4-hydroxy-3-acetylcoumarins, but with 2-hydroxy-4 : 5-dimethoxybenzoylacetone the results described in Part II (*loc. cit.*) were confirmed and a small yield of 4-hydroxy-3-acetyl-6 : 7-dimethoxycoumarin was invariably obtained. On the other hand, the carbonyl chloride method, *viz.*, the interaction of this reagent with the disodio-derivatives of *o*-hydroxybenzoylacetones, gave comparatively satisfactory yields of the requisite coumarins which were identical with the products obtained by the modified Anschütz method. It was recognised, however, that in the latter procedure the initial reaction product, of type (I), might well undergo cyclisation to give a chromone of type (X; R = Et or R = H) in place of the expected coumarin of type (III), and that the carbonyl chloride method was open to the same objection, *e.g.*, the intermediate of type (II), if formed, could cyclise in two ways.

In a search for a more rational and general synthetical route to 4-hydroxy-3-acetylcoumarins it was ultimately discovered that 4-hydroxycoumarins, of type (IV), can be conveniently *C*-acetylated in the 3-position by means of acetic anhydride and boron trifluoride. From the initial reaction products water precipitated boron chelate complexes of type (V) which, on hydrolytic decomposition under the appropriate conditions (see Experimental section), furnished compounds of type (III). Accordingly, from 4-hydroxy-, 4-hydroxy-6-methyl-, 4-hydroxy-6-methoxy-, 4-hydroxy-7-methoxy-, and 4-hydroxy-6 : 7-dimethoxy-coumarin the corresponding 4-hydroxy-3-acetylcoumarins were prepared by this method and, except in the case of *4-hydroxy-6-methoxy-3-acetylcoumarin* where a comparison was not possible, the products were identical with those from the modified Anschütz and the carbonyl chloride procedures, a result which clearly eliminates the possibility of the compounds prepared by the latter methods being 2-methylchromone-3-carboxylic acids of type (X; R = H). Consequently the compound *P*, formulated in Part II (*loc. cit.*) as 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid is 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin, and its piperonylidene derivative is *4-hydroxy-6 : 7-dimethoxy-3-(3 : 4-methylenedioxycinnamoyl)coumarin* (VI) and not the 2-styryl derivative of the isomeric chromone. This conclusion has been substantiated by a synthesis of *6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid* (X; R = H). Condensation of 2-hydroxy-4 : 5-dimethoxyacetophenone with ethyl oxalate by means of sodium gave rise to *ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate* (VII; R = H), the nature of which was clarified by cyclisation with alcoholic hydrochloric acid to *ethyl 6 : 7-dimethoxychromone-2-carboxylate.* Hydrolysis of the chromone and decarboxylation of the resulting *acid* gave 6 : 7-dimethoxychromone. Vigorous acetylation of (VII; R = H) furnished a small amount of *ethyl 4 : 5-dimethoxy-2-methylchromone-3-glyoxylate* accompanied by considerable amounts of ethyl 6 : 7-dimethoxychromone-2-carboxylate. The same glyoxylate (IX) was also formed by the foregoing method when (VII; R = H) was replaced by the *acetate* (VII, R = Ac), and more conveniently when (VII, R = H) was cyclised with acetic anhydride and boron trifluoride at 0°, a reaction which clearly proceeds by way of the intermediate (VIII; R = H). On treatment with warm concentrated sulphuric acid the glyoxylate (IX) was hydrolysed with the simultaneous evolution of carbon monoxide, giving rise to 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (X; R = H) which had the expected properties of a carboxylic acid and was readily differentiated from the isomeric 4-hydroxy-3-acetylcoumarin (III).



(VII.)



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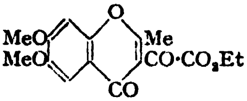
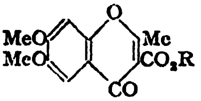


(IX.)



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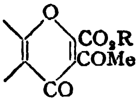


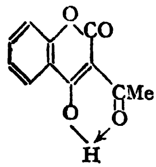
(XI.)

In the conversion of (VII; R = H or Ac) into (IX) by vigorous acetylation, a reaction which presumably proceeds by way of (VIII), cyclisation of this intermediate could lead, by an alternative route, to *ethyl 6 : 7-dimethoxy-3-acetylchromone-2-carboxylate* (XI; R = Et). Although with (VII; R = H) as the starting material ethyl 6 : 7-dimethoxy-3-acetylchromone-2-carboxylate (XI; R = Et) could not be isolated, the acetate (VII; R = Ac) gave a small amount of (XI; R = Et) which accompanied the main reaction product (IX). This compound (XI; R = Et) is readily distinguished from the isomeric ethyl 4 : 5-dimethoxy-2-methylchromone-3-glyoxylate by the fact that unlike the latter it does not evolve carbon monoxide on being heated with sulphuric acid and on hydrolysis with concentrated acid gave *6 : 7-dimethoxy-3-acetylchromone-2-carboxylic acid* (XI; R = H).

The 4-hydroxy-3-acetylcoumarins described in the present work melt without decomposition and are readily soluble in dilute aqueous sodium hydroxide. Unlike the parent 4-hydroxycoumarins, however, they dissolve but slowly in aqueous sodium hydrogen carbonate and apparently cannot be readily methylated or acetylated under the usual conditions, although it may be noted that Anschütz (*loc. cit.*) claims to have prepared a methyl ether of 4-hydroxy-

3-acetyl-7-methylcoumarin. With 2 : 4-dinitrophenylhydrazine sulphate solution 4-hydroxy-, 4-hydroxy-6-methyl-, and 4-hydroxy-7-methoxy-3-acetyl-coumarin reacted readily under the usual conditions, yielding the corresponding 2 : 4-dinitrophenylhydrazones, but 4-hydroxy-6-methoxy-3-acetylcoumarin reacted extremely slowly, whilst, as indicated in Part II (*loc. cit.*), 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin did not form a dinitrophenylhydrazone. Treatment of the 4-hydroxy-3-acetylcoumarins with warm 80% sulphuric acid caused extrusion of the *C*-acetyl group and gave rise to the corresponding 4-hydroxycoumarins.

The properties of 4-hydroxy-3-acetylcoumarins are in keeping with the view that the molecule contains a hydrogen-bonded system involving a comparatively stable 6-atom ring of which the two formulæ (XII) and (XIII) represent the unperturbed forms of the resonating system. Substituents in the benzenoid ring appear to affect materially the stability of the chelate system.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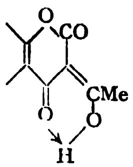
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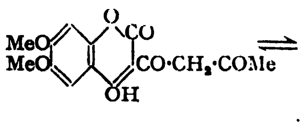
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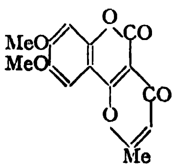
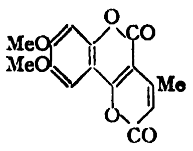

(XV.)


(XVI.)

When it became clear that the hydrolytic product, m. p. 208°, from *O*-dimethylcitromycinone could not be 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III), a re-examination of the compound was undertaken. The analytical results do not materially differ from the theoretical values required for (III) or for a *C*-acetyl derivative of this coumarin. On this account, combined with the fact that unlike (III) it readily formed a 2 : 4-dinitrophenylhydrazone, we concluded that the compound, m. p. 208°, was *4-hydroxy-6 : 7-dimethoxy-3-acetoacetylcoumarin* (XIV) which was confirmed when it was found that cyclisation with warm sulphuric acid regenerated *O*-dimethylcitromycinone, identical with the product obtained by the oxidation of *O*-dimethylcitromycin. Since, in the conversion of (XIV) into *O*-dimethylcitromycinone, it is reasonably certain that the readily enolisable 4-carbonyl group (the 4-hydroxyl group of the coumarin system) was involved in the cyclisation and not the more stable carbonyl group of the lactone system, *O*-dimethylcitromycinone has the angular structure (XV) and not the linear formula proposed in Part III (*loc. cit.*). Mr. G. W. K. Cavill of this Department (private communication), who has examined the decomposition of *O*-dimethylcitromycinol (Part III, *loc. cit.*), has independently concluded that *O*-dimethylcitromycin as well as the primary oxidation products have angular structures corresponding to (XV), possibilities which were envisaged but not supported in Part III. Detailed experimental evidence in support of this revised structure for *O*-dimethylcitromycin and its derivatives will be discussed in a subsequent communication.

During numerous exploratory experiments on the synthesis of the diketone (XIV) and hence of *O*-dimethylcitromycinone (XV) it was found that 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin could not be *C*-acetylated to give (XIV) [or its cyclisation product (XV)] by boron trifluoride–acetic anhydride, the Claisen reaction, or the Kostanecki vigorous-acetylation process. The alternative route of forming the γ-pyrone ring in (XV) by the condensation of acetoacetic acid or its ester with 4-hydroxy-6 : 7-dimethoxycoumarin was attempted but, as expected, with the usual condensing agents (concentrated sulphuric acid, phosphoric oxide, or phosphorus oxychloride) this reaction gave only *6 : 7-dimethoxy-4′-methyl-α-pyrono(5′ : 6′ : 3 : 4)coumarin* (XVI) isomeric with *O*-dimethylcitromycinone. The failure of (XVI) to dissolve in concentrated hydrochloric acid or to form salts, and its behaviour with dilute aqueous sodium hydroxide, is in keeping with the α-pyrono-coumarin structure and readily serves to distinguish the compound from *O*-dimethylcitromycinone.

EXPERIMENTAL.

4-Hydroxy-3-acetylcoumarin.—(*a*) Ethyl acetoacetate (3·8 ml.), dissolved in ether (20 ml.), was added to ethereal sodium ethoxide (from 0·7 g. of sodium, 5 ml. of alcohol, and 20 ml. of ether), followed by a solution of *o*-acetoxybenzoyl chloride (from 5 g. of acid) in ether (10 ml.), and the mixture warmed under reflux for 1 hour. More sodium ethoxide (from 0·7 g. of sodium) in a mixture of alcohol and ether (10 ml.) was added to the reaction mixture which became yellow and then deposited a yellow precipitate. The reaction was completed by warming the mixture for a further 3 hours and on isolation the solid was washed with ether, dried, and dissolved in water (150 ml.). Acidification of this solution with concentrated hydochloric acid gave 4-hydroxy-3-acetylcoumarin (2·9 g.) which formed needles, m. p. 138·5°, from alcohol (cf. Anschütz, *Annalen*, 1909, **367**, 194, who gives m. p. 134°).

(*b*) After the initial reaction between *o*-hydroxyacetophenone (5 g.), pulverised sodium (4 g.), and ethyl acetate (30 ml.) had somewhat subsided the mixture was heated on the water-bath for ½ hour, cooled, and treated with crushed ice (25 g.). The sodio-derivative of salicyloylacetone, which separated, was collected, washed with a little ice-water and then ether, and decomposed with dilute acetic acid, giving the diketone (3·2 g.) which formed square colourless prisms from alcohol, or plates, m. p. 95°, from light petroleum, and had a reddish-brown ferric reaction in alcohol (Found: C, 67·2; H, 5·6. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%) (Wittig, Bangert, and Richter, *Annalen*, 1926, **446**, 155, record m. p. 90·5—91·5°). Cyclisation of this ketone with sulphuric acid gave an almost theoretical yield of 2-methylchromone, m. p. 71° (Block and Kostanecki, *Ber.*, 1900, **33**, 1999, give m. p. 70—71°).

The foregoing diketone (5 g.) was added to a solution of sodium ethoxide (from 1·6 g. of sodium) in alcohol (50 ml.), the greater part of the solvent was distilled in a vacuum, and the disodio-derivative was precipitated from the cooled residue by means of ether (200 ml.), washed and dried (yield, 6·4 g. of a lemon-yellow powder). A slow stream of carbonyl chloride was led into a suspension of this derivative (5 g.) in toluene (75 ml.) cooled with ice–salt. The liquid became scarlet and next day the mixture was filtered, the sodium chloride was washed with a little toluene, and the combined filtrate and washings were concentrated by evaporation of most of the toluene in a vacuum. On being kept the residue deposited 4-hydroxy-3-acetylcoumarin which was washed with ether and obtained as a yellow crystalline powder (0·7 g.). Purified from alcohol, the compound had m. p. and mixed m. p. 138·5°. The 2 : *4-dinitrophenylhydrazone*, which is very sparingly soluble in the usual organic solvents, separated from nitrobenzene in orange plates, m. p. 271° (decomp.) (Found: N, 14·9. $C_{17}H_{12}O_7N_4$ requires N, 14·6%).

(*c*) When boron trifluoride (from 22 g. of potassium fluoroborate) was slowly led into a mixture of acetic acid (5 ml.), acetic anhydride (2 g.), and 4-hydroxycoumarin (Boyd and Robertson, *J.*, 1948, 174) (1 g.) kept at room temperature, the solid quickly dissolved and next day the pale yellow viscous liquid was poured into water (100 ml.). After having been collected, thoroughly washed with water, and dried, the resulting fawn-coloured crystalline precipitate (1·2 g.) was decomposed with boiling 95% alcohol (50 ml.), and on cooling the mixture deposited 4-hydroxy-3-acetylcoumarin in long needles, m. p. and mixed m. p. 138°, identical with specimens prepared by methods (*a*) and (*b*). This coumarin dissolves slowly in aqueous sodium hydrogen carbonate and gives a yellow colour with alcoholic ferric chloride which becomes orange when the mixture is warmed. The 2 : 4-dinitrophenylhydrazone formed orange leaflets, m. p. and mixed m. p. 271° (decomp.), from nitrobenzene.

A mixture of 4-hydroxy-3-acetylcoumarin (0·2 g.), alcoholic sodium ethoxide (from 0·03 g. of sodium and 10 ml. of alcohol), and piperonal (0·15 g.) was warmed on the steam-bath for 30 minutes and the cooled orange reaction mixture poured into 2N-hydrochloric acid (20 ml.). Crystallisation of the resulting precipitate from acetic acid gave the *piperonylidene* derivative in orange needles (0·18 g.), m. p. 252° after sintering at 248° (Found: C, 67·6; H, 3·8. $C_{19}H_{12}O_6$ requires C, 67·9; H, 3·6%).

4-Hydroxy-3-acetyl-6-methylcoumarin.—(*a*) Prepared by the modification of Anschütz and Sieber's method (*Annalen*, 1909, **367**, 250) employed for the preparation of 4-hydroxy-3-acetylcoumarin, 4-hydroxy-3-acetyl-6-methylcoumarin had m. p. 147·5°, and gave a yellow ferric reaction in alcohol; yield, 1·7 g. from 5 g. of 2-acetoxy-5-methylbenzoyl chloride (Found: C, 66·0; H, 4·6. Calc. for $C_{12}H_{10}O_4$: C, 66·0; H, 4·6%).

(*b*) Interaction of the disodio-derivative of 2-hydroxy-5-methylbenzoylacetone (Baker, *J.*, 1933, 1381) (5 g.) with excess of carbonyl chloride in toluene (75 ml.) gave rise to 4-hydroxy-3-acetyl-6-methylcoumarin (0·7 g.), m. p. and mixed m. p. 147·5°. The 2 : *4-dinitrophenylhydrazone* formed clusters of orange needles from nitrobenzene or orange prisms, m. p. 265° (decomp.), from acetic acid (Found: N, 14·5. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

(*c*) The boron complex, m. p. 228° (decomp.), formed by the interaction of 4-hydroxy-6-methylcoumarin (Boyd and Robertson, *loc. cit.*) (1 g.), acetic acid (3 ml.), acetic anhydride (2 g.), and excess of boron trifluoride, was dissolved in boiling alcohol. On cooling, the solution deposited 4-hydroxy-3-acetyl-6-methylcoumarin as a mixture of rods and diamond-shaped prisms (0·9 g.), m. p. 148° after slight sintering at 140°, unchanged on further purification (Found: C, 66·1; H, 4·6%). The 2 : 4-dinitrophenylhydrazone had m. p. 264° (decomp.). Prepared by the method employed in the case of 4-hydroxy-3-acetylcoumarin, the *piperonylidene* derivative from 4-hydroxy-6-methyl-3-acetylcoumarin (0·2 g.) formed small orange needles (0·19 g.), m. p. 260—261°, from acetic acid and gave a violet colour with concentrated sulphuric acid (Found: C, 68·4; H, 4·1. $C_{20}H_{14}O_6$ requires C, 68·6; H, 4·0%).

4-Hydroxy-7-methoxy-3-acetylcoumarin.—(*a*) This *coumarin* (2·6 g.) was prepared from 2-hydroxy-4-methoxybenzoyl chloride (from 6·5 g. of acid) by the modified Anschütz method and on crystallisation from alcohol and then ethyl acetate–light petroleum (b. p. 80—100°) was obtained in yellowish-cream-coloured needles, m. p. 187·5°, giving a golden-yellow ferric reaction in alcohol which became red on warming (Found: C, 61·5; H, 4·7. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

(*b*) Interaction of the disodio-derivative of 2-hydroxy-4-methoxybenzoylacetone (Kostanecki and Lloyd, *Ber.*, 1901, **34**, 2942) (2·5 g.) with excess of carbonyl chloride in toluene (40 ml.) during 24 hours furnished 4-hydroxy-7-methoxy-3-acetylcoumarin (1·1 g.), m. p. 187·5°, after purification from alcohol. The 2 : *4-dinitrophenylhydrazone* formed small red needles, m. p. 255°, from nitrobenzene (Found: N, 13·8. $C_{18}H_{14}O_8N_4$ requires N, 13·5%). When subjected to the standard method for the preparation of a piperonylidene derivative, almost all the 4-hydroxy-7-methoxy-3-acetylcoumarin was recovered unchanged.

(*c*) *4-Acetoxy-7-methoxycoumarin* was prepared by the acetylation of 4-hydroxy-7-methoxycoumarin (Boyd and Robertson, *loc. cit.*) (4 g.) with hot acetic anhydride (40 ml.) during 1 hour and on isolation crystallised from alcohol in flat needles (4 g.), m. p. 133—134°, insoluble in aqueous sodium hydrogen carbonate (Found: C, 61·7; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). Interaction of the acetate (1 g.) with acetic acid (3 ml.), acetic anhydride (2 g.), and excess of boron trifluoride was accompanied by deacetylation and gave 4-hydroxy-7-methoxy-3-acetylcoumarin, m. p. 189, identical with specimens prepared by methods (*a*) and (*b*) (Found: C, 61·1; H, 4·4%). The 2 : 4-dinitrophenylhydrazone had m. p. 262° (decomp.) after sintering at 255°.

4-Hydroxy-6-methoxycoumarin.—When the vigorous reaction (initiated by gentle warming) between

2-hydroxy-5-methoxyacetophenone (Kostanecki and Lampe, *Ber.*, 1904, **37**, 774) (1·4 g.), ethyl carbonate (20 ml.), and pulverised sodium (0·4 g.) had somewhat subsided, the mixture was heated on the steam-bath for 1 hour, cooled, treated with a little methanol, and diluted with much ether. On isolation the solid was washed with ether and decomposed with excess of dilute hydrochloric acid, giving 4-*hydroxy-6-methoxycoumarin* which formed colourless needles (1·6 g.), m. p. 170° (decomp.), from dilute alcohol, soluble in aqueous sodium hydrogen carbonate (Found: C, 62·5; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%).

4-*Hydroxy-6-methoxy-3-acetylcoumarin*.—Interaction of the foregoing coumarin (0·7 g.), acetic acid (6 ml.), acetic anhydride (1·4 g.), and excess of boron trifluoride in the usual manner gave a solid (0·8 g.), m. p. ~180°, which on being dissolved in boiling alcohol yielded 4-*hydroxy-6-methoxy-3-acetylcoumarin*. This compound separated from the cooled solution in long silky needles, changing to small prisms when left in contact with the solvent and, on recrystallisation from acetic acid, formed elongated rectangular prisms, m. p. 153°, slowly soluble in aqueous sodium hydrogen carbonate and giving an orange-yellow ferric reaction in alcohol (Found: C, 61·2; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). Prepared under the usual conditions, the 2 : 4-*dinitrophenylhydrazone* was very slowly formed and after being extracted with boiling alcohol the crude product crystallised from nitrobenzene in orange rectangular plates, m. p. 246—247° (Found: C, 52·5; H, 3·6. $C_{18}H_{14}O_8N_4$ requires C, 52·2; H, 3·4%).

4-*Hydroxy-6 : 7-dimethoxy-3-acetylcoumarin* (III).—(*a*) The interaction of 2-acetoxy-4 : 5-dimethoxybenzoyl chloride [from 5 g. of 2-acetoxy-4 : 5-dimethoxybenzoic acid (Head and Robertson, *J.*, 1931, 2432)], and ethyl sodioacetoacetate (from 3 ml. of ester and 0·52 g. of sodium) in ether (20 ml.), followed by treatment of the mixture with warm alcoholic sodium ethoxide (from 0·52 g. of sodium and 15 ml. of alcohol) in ether (50 ml.) on the water-bath for 3 hours, gave 4-*hydroxy-6 : 7-dimethoxy-3-acetylcoumarin* which separated from alcohol in lemon-yellow needles, m. p. 250° (Found: C, 59·7; H, 4·6. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

(*b*) The foregoing coumarin was formed by the action of excess of carbonyl chloride on the disodio-derivative of 2-hydroxy-4 : 5-dimethoxybenzoylacetone (Part II, *loc. cit.*) in toluene cooled in an ice-salt bath during 24 hours. The product formed pale yellow needles (1·5 g.), m. p. and mixed m. p. 250°.

(*c*) Obtained by the interaction of 4-hydroxy-6 : 7-dimethoxycoumarin (1 g.), acetic anhydride (2 g.), and excess of boron trifluoride in acetic acid (5 ml.), the viscous reaction mixture was treated with water (50 ml.), and the bright yellow precipitate (1·1 g.) isolated, washed, and dried. On being cooled a solution of the product in hot acetic acid deposited the unchanged boron complex in yellow needles, m. p. 280°, insoluble in cold 2N-aqueous sodium hydroxide and giving a green flame test. When this compound was boiled with 50% aqueous sodium acetate or with sodium acetate in acetic acid, a colourless solution was slowly formed which, on being cooled, deposited 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin in cream-coloured needles (0·8 g.), m. p. and mixed m. p. 250°. This compound, which gave a golden-yellow colour with ferric chloride in aclohol and slowly dissolved in aqueous sodium hydrogen carbonate, did not appear to form a 2 : 4-dinitrophenylhydrazone.

Ethyl 2-Hydroxy-4 : 5-dimethoxybenzoylpyruvate (VII; R = H).—When a well agitated mixture of 2-hydroxy-4 : 5-dimethoxyacetophenone (Part II, *loc. cit.*) (5 g.), ethyl oxalate (15 ml.), and pulverised sodium (0·8 g.), containing one drop of alcohol, was heated on the steam-bath, a vigorous reaction ensued and the reaction mixture set to a stiff paste. After the addition of sufficient methanol to destroy unchanged sodium, followed by an excess of ether, the sodio-derivative was collected, washed with ether, mixed with acetic acid (10 ml.), and then treated with a considerable volume of water. Thus precipitated, *ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate* was collected and crystallised from aqueous alcohol, forming small yellow needles (4·9 g.), m. p. 157°, which give an olive-green, amber-tinged ferric reaction in alcohol (Found: C, 56·9; H, 5·6. $C_{14}H_{16}O_7$ requires C, 56·7; H, 5·4%).

A solution of this ester (3 g.) in pyridine (7 ml.) and acetic anhydride (10 ml.) was kept at room temperature for 18 hours and then mixed with an excess of dilute hydrochloric acid, giving a viscous precipitate which slowly solidified. Crystallised from alcohol this gave *ethyl 2-acetoxy-4 : 5-dimethoxy benzoylpyruvate* (VII; R = Ac) in pale lemon-yellow, feathery needles (2 g.), m. p 133°, exhibiting a reddish-brown ferric reaction in alcohol (Found: C, 56·9; H, 5·4. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·3%).

A solution of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (1 g.) in the minimum quantity of warm acetic acid was treated with a drop of concentrated hydrochloric acid, heated on the steam-bath for 15 minutes, and then poured on ice, giving a precipitate of *ethyl 6 : 7-dimethoxychromone-2-carboxylate* which, on crystallisation from alcohol or ethyl acetate–light petroleum (b. p. 60—80°), formed tiny, cream-coloured needles (0·88 g.), m. p. 182° (Found: C, 60·2; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·2; H, 5·1%). When a solution of this chromone-ester (5 g.) in hot alcohol (50 ml.) was mixed with concentrated hydrochloric acid (25 ml.) and then heated under reflux for 3 hours 6 : 7-*dimethoxychromone-2-carboxylic acid* gradually separated. On isolation from the cooled mixture, this compound was purified by crystallisation from hot nitrobenzene and obtained in tiny, pale cream-coloured needles (3·5 g.), m. p. 303° (decomp.), readily soluble in cold aqueous sodium hydrogen carbonate and insoluble in the usual organic solvents (Found: C, 57·8; H, 4·2. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). On being heated above its melting point this acid (1 g.) readily evolved carbon dioxide, leaving a residue of 6 : 7-dimethoxychromone which was purified by sublimation in a high vacuum at 180° and obtained in small irregular, almost colourless prisms (0·6 g.), m. p. 163°, from light petroleum (b. p. 60—80°), identical with an authentic specimen (Part II, *loc. cit.*).

Ethyl 2-Methyl-6 : 7-dimethoxychromone-3-glyoxylate (IX).—(*a*) A mixture of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (6 g.), sodium acetate (6 g.), and acetic anhydride (30 ml.) was heated on the steam-bath for 15 minutes, treated with water (100 ml.), and then warmed until a clear solution was obtained. On being kept at 0° the reaction mixture slowly deposited ethyl 6 : 7-dimethoxychromone-2-carboxylate (3·2 g.) and, after the separation of the latter, the liquor on the addition of water (200 ml. and then 300 ml.) deposited more ethyl 6 : 7-dimethoxychromone-2-carboxylate (0·5 g.), followed by *ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate* (IX) (*ca.* 0·5 g.). Although the glyoxylate separated in this manner in two experiments, in a number of cases it failed to do so and was isolated from the diluted liquor by extraction with ethyl acetate. Repeated crystallisation of the crude glyoxylate from alcohol, benzene–light petroleum (b. p. 60—80°), and finally ethyl acetate gave the compound in almost colourless tiny needles, m. p. 182°, which on admixture with ethyl 6 : 7-dimethoxychromone-2-carboxylate had m. p. ~160° (Found : C, 59·8; H, 4·9. $C_{16}H_{16}O_7$ requires C, 60·0; H, 5·0%). The *semicarbazone* separated from water in small colourless prisms, m. p. 240° (decomp.) (Found : N, 10·7. $C_{17}H_{19}O_7N_3$ requires N, 11·1%).

(*b*) A mixture of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (3 g.), acetic anhydride (11 ml.), and acetic acid (5 ml.) was saturated at 0° with boron trifluoride, and 24 hours later the orange-red complex was collected, washed with acetic acid, and warmed with acetic acid (17 ml.), water (7 ml.), and sodium acetate (7 g.). The resulting homogeneous solution was then diluted with water (250 ml.), and next day the gummy semi-crystalline product was collected and purified by crystallisation as in method (*a*), giving a small yield of ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate, m. p. and mixed m. p. 182°.

(*c*) When a mixture of ethyl 2-acetoxy-4 : 5-dimethoxybenzoylpyruvate (2 g.), sodium acetate (2 g.), and acetic anhydride (10 ml.) was warmed on the steam-bath for 5 minutes and diluted with water (150 ml.), a semi-crystalline solid (2 g.) separated which, on repeated purification from alcohol, benzene, and ethyl acetate, gave a small yield of ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate, m. p. and mixed m. p. 182°.

Evaporation of the mother-liquors from the purification of the foregoing chromone-3-glyoxylate prepared by method (*c*), followed by slow crystallisation of the residue from ethyl acetate, gave *ethyl* 6 : 7-*dimethoxy*-3-*acetylchromone*-2-*carboxylate* (XI; R = Et) in thick, massive, colourless prisms (0·5 g.), m. p. 147°, after repeated purification (Found : C, 60·0; H, 5·0%). This compound (0·2 g.), which had a negative ferric reaction, was warmed on the steam-bath with concentrated sulphuric acid (3 ml.) for 5 minutes, the solution was treated with crushed ice, and the resulting precipitate was isolated by extraction with much chloroform. Crystallisation of the product from the same solvent yielded 6 : 7-*dimethoxy*-3-*acetylchromone*-2-*carboxylic acid* (XI; R = H) in colourless prisms (0·15 g.), m. p. 240—241° (decomp.), sparingly soluble in alcohol or chloroform, almost insoluble in benzene or light petroleum, readily soluble in 2N-aqueous sodium hydrogen carbonate (Found : C, 57·4; H, 4·2. $C_{14}H_{12}O_7$ requires C, 57·5; H, 4·1%). Decarboxylation of this acid appeared to give a mixture of non-acidic compounds which was not further investigated.

When heated on the steam-bath with concentrated sulphuric acid (5 ml.), ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate (0·5 g.) evolved carbon monoxide and, after the effervescence had ceased, the reaction mixture was treated with ice. Crystallisation of the resulting precipitate from acetic acid (charcoal) or from chloroform–light petroleum (b. p. 60—80°) gave 6 : 7-*dimethoxy*-2-*methylchromone*-3-*carboxylic acid* in tiny colourless needles (0·38 g.), m. p. 224° (decomp.) (Found : C, 59·0; H, 4·5. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

[With G. W. K. CAVILL.] 4-*Hydroxy*-6 : 7-*dimethoxy*-3-*acetoacetylcoumarin* (XIV).—A solution of *O*-dimethylcitromycinone (Part III, *loc. cit.*) (1 g.) in concentrated hydrochloric acid (50 ml.) was heated on the steam-bath for 10 minutes, diluted with water (100 ml.), almost neutralised with 2N-aqueous sodium hydroxide, and extracted with ether (50 ml. × 5). During the extraction unchanged *O*-dimethylcitromycinone (0·8 g.), which is insoluble in ether, separated from the aqueous liquor. Evaporation of the dried ethereal extract left 4-*hydroxy*-6 : 7-*dimethoxy*-3-*acetoacetylcoumarin* which formed colourless needles (0·05 g.), m. p. 208° (decomp.), from ethanol (Found : C, 58·8; H, 4·7. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%).

The yellow solution of the compound (0·04 g.) in concentrated sulphuric acid (2 ml.) was kept at room temperature for 24 hours and then poured into ice-water (30 ml.). The pale yellow solid, which slowly separated, was collected, well washed, and crystallised from acetic acid, giving *O*-dimethylcitromycinone in colourless prisms (0·02 g.), m. p. 314—316° (decomp.), undepressed on admixture with an authentic specimen.

6 : 7-*Dimethoxy*-4′-*methyl*-α-*pyrono*(5′ : 6′ : 3 : 4)*coumarin* (XVI).—A mixture of 4-hydroxy-6 : 7-dimethoxycoumarin (1 g.), phosphoric oxide (4 g.), ethyl acetoacetate (2 ml.), and acetic acid (20 ml.) was heated on the steam-bath for 20 minutes and the resulting brownish semi-solid was transferred portion-wise to an excess of water. After having been well washed with aqueous sodium hydrogen carbonate and water the resulting crystalline product was extracted with concentrated hydrochloric acid and then recrystallised from acetic acid (charcoal), giving the α-*pyrono-coumarin* in pale cream-coloured, thin prisms (0·9 g.), m. p. 292° (slight decomp.) [Found : C, 62·6; H, 4·3; OMe, 21·7. $C_{13}H_6O_4(OMe)_2$ requires C, 62·5; H, 4·2; OMe, 21·5%]. This compound dissolves slowly in hot 2N-aqueous sodium hydroxide and is precipitated unchanged on acidification of the yellow alkaline solution with dilute hydrochloric acid. An acetic acid solution of the coumarin exhibits an intense purple fluorescence.

When the phosphoric oxide was replaced by phosphorus oxychloride in the foregoing reaction the yield of coumarin was 0·35 g., whilst with concentrated sulphuric acid only a very small amount of the compound was formed.

UNIVERSITY OF LIVERPOOL. [*Received, December 12th,* 1949.]

184. 1 : 4-*Oxazines. Part I. Synthesis of Hydroxy*-1 : 4-*oxazines.*

By G. T. Newbold, F. S. Spring, and Wilfred Sweeny.

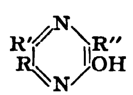
A simple method for the synthesis of 1 : 4-oxazine derivatives is described in which an α-bromoacyl derivative (VII) of ethyl α-amino-β-ketobutyrate is treated with ammonia or sodium ethoxide. In this way, ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (VIII; R = Me, R' = Et) and ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (VIII; R = H, R' = Et) have been prepared. The esters can be hydrolysed to the corresponding acids (VIII; R' = H) which when heated lose carbon dioxide to yield the hydroxy-1 : 4-oxazines (IX).

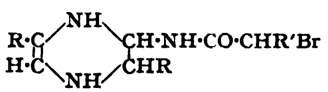
Treatment of an α-bromoacyl derivative (I) of an α-amino-ketone of the type NH$_2$·CHR·COR' (in which R is not hydrogen) with ammonia gives a hydroxypyrazine (II) (Tota and Elderfield, *J. Org. Chem.*, 1942, **7**, 317; Newbold and Spring, *J.*, 1947, 373). Similar treatment of an α-bromoacyl derivative (III) of an aminomethyl ketone, however, gives a 2-acylamidopyrazine (VI) (Newbold, Spring, and Sweeny, *J.*, 1948, 1855; 1949, 300). The mechanism proposed for the latter reaction involves the self-condensation of the aminomethyl ketone derivative (III) to give a tetrahydropyrazine (IV) which is converted by an intramolecular reductive dehalogenation into a dihydropyrazine such as (V), oxidation of which gives the aromatic pyrazine (VI). This mechanism is in accord with the observation that this type of reaction only takes place with aminomethyl ketone derivatives and that it requires the presence of a halogen substituent in the acyl group. Furthermore, in one instance the dihydropyrazine intermediate was sufficiently stable to allow its isolation.

(I.) R'·CO·CHR·NH·CO·CHR''Br

R·CO·CH$_2$·NH·CO·CHR'Br (III.)

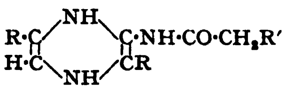
(II.)

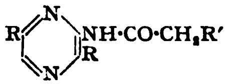




(IV.)

(V.)

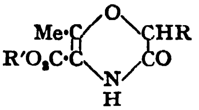




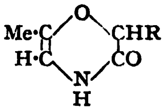
(VI.)

Me·CO·CH(CO$_2$Et)·NH·CO·CHRBr

(VII.)



(VIII.)



(IX.)

Since Tota and Elderfield's direct method could not be applied to the synthesis of 3 : 5-disubstituted 2-hydroxypyrazines, an examination was made of the action of ammonia on an α-bromoacyl derivative of type (I) in which R is a group capable of elimination after ring-closure is complete; the object of this approach was to enforce 2-hydroxypyrazine formation and exclude 2-acylamidopyrazine formation by temporary protection of the methylene group essential for the latter reaction. The present paper records our experience with α-bromoacyl derivatives (VII) of ethyl α-amino-β-ketobutyrate (ethyl α-aminoacetoacetate).

Acylation of this ester with α-bromopropionyl chloride in the presence of *N*-methylmorpholine gives ethyl α-(α-bromopropionamido)-β-ketobutyrate (VII; R = Me). Treatment of the last compound with liquid ammonia at room temperature gives neither a hydroxypyrazine nor an acylamidopyrazine but a 1 : 4-oxazine derivative, ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (VIII; R = Me, R' = Et) by simple elimination of the elements of hydrogen bromide. This 1 : 4-oxazine derivative is more conveniently obtained by treatment of (VII; R = Me) with sodium ethoxide. Cautious alkaline hydrolysis of ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate gives the corresponding 1 : 4-oxazine-3-carboxylic acid (VIII; R = Me, R' = H) which when heated yields 3-hydroxy-2 : 6-dimethyl-1 : 4-oxazine (IX; R = Me).

In a similar manner treatment of ethyl α-bromoacetamido-β-ketobutyrate (VII; R = H) with ammonia or, better, sodium ethoxide yields ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (VIII; R = H, R' = Et), hydrolysed to 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid (VIII; R = R' = H) from which 5-hydroxy-2-methyl-1 : 4-oxazine (IX; R = H) is obtained by the action of heat.

Although tetrahydro-1 : 4-oxazines (morpholines) are well known, as are compounds such as phenoxazine containing the 1 : 4-oxazine system as part of a fused aromatic ring system, as far as we are aware simple 1 : 4-oxazine derivatives have not previously been described; Hill and Powell (*J. Amer. Chem. Soc.*, 1945, 67, 1462) have suggested that a dehydration product from a benzoyl derivative of 3 : 4-dihydroxyphenacylaminoethanol is a dihydro-1 : 4-oxazine, and Cook and Cox (*J.*, 1949, 2347; cf. Chadwick and Pacsu, *J. Amer. Chem. Soc.*, 1943, 65, 392) have described a series of 2 : 5-diketomorpholines.

The course of the reaction between ammonia and an α-(α-bromoacylamido)-ketone (I) is controlled by the nature of the substituent R; if this is a hydrogen atom, reaction proceeds to give a 2-acylamidopyrazine (VI). When R is an alkyl or aryl group, the reaction leads to a hydroxypyrazine (II) and, where R is the carbethoxy-group, it gives a 1 : 4-oxazine derivative. The formation of a 1 : 4-oxazine derivative is dependent upon a high degree of enolisation induced in the carbonyl group of the compounds (VII) by the neighbouring carbethoxyl group, a view supported by the observation that 3-(α-bromopropionamido)butan-2-one, which on treatment with ammonia gives 3-hydroxy-2 : 5 : 6-trimethylpyrazine (Newbold and Spring, *loc. cit.*), on reaction with sodium ethoxide gives 3-(α-ethoxypropionamido)butan-2-one and not 5-hydroxy-2 : 3 : 6-trimethyl-1 : 4-oxazine. Similarly, treatment of either α-bromopropionamidoacetone or ω-(α-bromopropionamido)acetophenone with sodium ethoxide in each case leads to simple replacement of halogen by an ethoxy-group to give α-ethoxypropionamidoacetone and ω-(α-ethoxypropionamido)acetophenone, respectively. In each case the yield of ethoxy-derivative is high and in neither case is the formation of a 1 : 4-oxazine observed.

EXPERIMENTAL.

Ethyl α-(α-Bromopropionamido)-β-ketobutyrate.—A stirred suspension of ethyl α-amino-β-ketobutyrate hydrochloride (10·0 g.) in dry chloroform (150 c.c.), to which was added a solution of α-bromopropionyl chloride (11·0 g.) in dry chloroform (50 c.c.), was cooled to 0° and treated with *N*-methylmorpholine (13·0 g.) in dry chloroform (25 c.c.) added dropwise during 30 minutes; the reaction mixture was stirred for 1 hour at 0°, then washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4), and the chloroform removed under reduced pressure. The residue, which solidified, was crystallised from light petroleum (b. p. 40—60°), from which *ethyl α-(α-bromopropionamido)-β-ketobutyrate* (13·0 g., 84%) separated as needles, m. p. 70° (Found : C, 38·5; H, 5·0; N, 5·0. $C_9H_{14}O_4NBr$ requires C, 38·6; H, 5·0; N, 5·0%).

Ethyl α-Bromoacetamido-β-ketobutyrate.—The method described above being used, ethyl α-amino-β-ketobutyrate hydrochloride (13·5 g.) was treated with bromoacetyl chloride (15·0 g.) in the presence of *N*-methylmorpholine (20·0 g.) to give *ethyl α-bromoacetamido-β-ketobutyrate* (16·5 g., 83%), which separated from light petroleum (b. p. 80—100°) as needles, m. p. 99° (Found: C, 36·2; H, 4·5; N, 5·1. $C_8H_{12}O_4NBr$ requires C, 36·1; H, 4·5; N, 5·3%). Both acylamidoketobutyrates are insoluble in water, readily soluble in the common organic solvents, and give a claret-red colour with aqueous ethanolic ferric chloride solution.

Ethyl 5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate.—(*a*) A solution of ethyl α-(α-bromopropionamido)-β-ketobutyrate (10·0 g.) in liquid ammonia (100 c.c.) containing ammonium iodide (0·5 g.) was kept in an autoclave at 15° for 16 hours. After removal of the ammonia, the residue was extracted (Soxhlet) with light petroleum (b. p. 60—80°). Concentration of the extract gave *ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate* (4·3 g., 61%) as needles, m. p. 96° (Found : C, 54·1, 54·3; H, 6·5, 6·8; N, 7·3, 6·8. $C_9H_{13}O_4N$ requires, C, 54·3; H, 6·5; N, 7·0%). Light absorption (ethanol) : Maxima at 2300 A. (ε = 7100) and 2800 A. (ε = 5600).

(*b*) A solution of ethyl α-(α-bromopropionamido)-β-ketobutyrate (0·80 g.) in ethanol (2 c.c.) was added to a solution of sodium ethoxide, from sodium (0·07 g.) and ethanol (2 c.c.). After being kept overnight at 15° the solvent was removed under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 60—80°; 3 × 10 c.c.). Ethyl 5-hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylate (0·4 g.) separated on cooling as needles, m. p. 96° alone or mixed with the specimen described under (*a*).

Ethyl 5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate.—(*a*) Ethyl α-bromoacetamido-β-ketobutyrate (5·1 g.) was treated with liquid ammonia as described above. Removal of the ammonia gave a gummy residue which was extracted with light petroleum (b. p. 80—100°; 6 × 25 c.c.); concentration of the extract under reduced pressure gave *ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate* (0·5 g., 14%) as needles, m. p. 112° (Found : C, 51·6; H, 5·9; N, 7·85. $C_8H_{11}O_4N$ requires C, 51·9; H, 5·9; N, 7·6%). Light absorption (ethanol) : Maxima at 2300 A. (ε = 6800) and 2800 A. (ε = 5400).

(*b*) Ethyl α-bromoacetamido-β-ketobutyrate (4·1 g.) in dry ethanol (25 c.c.) was treated with a solution of sodium ethoxide, from sodium (0·4 g.) and ethanol (5 c.c.), at 15° and kept at this temperature for 16 hours. Evaporation of the ethanol under reduced pressure and extraction (Soxhlet) of the residue with light petroleum (b. p. 60—80°) gave ethyl 5-hydroxy-2-methyl-1 : 4-oxazine-3-carboxylate (1·55 g., 54·5%) as needles, m. p. 112° either alone or when mixed with the specimen prepared by method (*a*).

5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic Acid.—A suspension of ethyl 5-hydroxy-2 : 6-dimethyloxazine-3-carboxylate (3·0 g.) in aqueous sodium hydroxide (150 c.c.; 0·1N.) was shaken at 15°. After 16 hours, when dissolution was complete, the mixture was acidified to pH 4·0 with hydrochloric acid and evaporated under reduced pressure to half-bulk. After cooling to 5° the crystalline solid was separated, washed with ethanol, and dried in air (2·15 g., 83%). *5-Hydroxy-2 : 6-dimethyl-1 : 4-3-carboxylic acid* separates from methanol as prisms, m. p. 214° (decomp.) (Found : C, 49·6; H, 5·6; N, 8·5%; equiv., 172. $C_7H_9O_4N$ requires C, 49·1; H, 5·3; N, 8·2%; equiv., 171). Light absorption (ethanol): Maxima at 2300 A. (ε = 7100) and 2800 A. (ε = 5900).

5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid was similarly obtained from its ethyl ester in 64% yield. It crystallised from methanol as prisms, m. p. 226° (decomp.) (Found : C, 46·1; H, 4·3; N, 9·4%; equiv., 161. $C_6H_7O_4N$ requires C, 45·9; H, 4·5; N, 8·9%; equiv., 157). Light absorption (ethanol): Maxima at 2260 A. (ε = 6900) and 2800 A. (ε = 5800).

3-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine.—5-Hydroxy-2 : 6-dimethyl-1 : 4-oxazine-3-carboxylic acid (200 mg.) was heated to 235° at atmospheric pressure for 15 minutes, effervescence then having ceased. Sublimation of the residue at 120°/1 mm. gave *3-hydroxy-2 : 6-dimethyl-1 : 4-oxazine* as plates, m. p. 73° (40 mg.) (Found : C, 56·8; H, 7·15; N, 10·9. $C_6H_9O_2N$ requires C, 56·7; H, 7·1; N, 11·0%). Light absorption (ethanol): Maximum at 2680 A. (ε = 3800). The compound, which is extremely hygroscopic, is soluble in the cold in the common solvents with the exception of light petroleum.

5-Hydroxy-2-methyl-1 : 4-oxazine.—5-Hydroxy-2-methyl-1 : 4-oxazine-3-carboxylic acid (100 mg.) was kept at 250° for 15 minutes at atmospheric pressure. The product was distilled at 120°/3 mm. to give a colourless oil, which solidified. Sublimation at 80°/0·5 mm. gave *5-hydroxy-2-methyl-1 : 4-oxazine* (20 mg.) as hygroscopic prisms, m. p. 54—55° (Found : C, 52·95; H, 6·4; N, 12·3. $C_5H_7O_2N$ requires C, 53·2; H, 6·2; N, 12·4%). Light absorption (ethanol): Maximum at 2680 A. (ε = 4300).

3-(α-Ethoxypropionamido)butan-2-one.—A solution of 3-(α-bromopropionamido)butan-2-one (1·5 g.) in dry ethanol (15 c.c.) was added to a cold solution of sodium ethoxide, from sodium (0·2 g.) and ethanol (5 c.c.), and kept at 15° for 36 hours. The red solution was separated from sodium bromide and evaporated to dryness under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 80—100°; 3 × 5 c.c.). Removal of the solvent from the extract gave an oil which solidified on cooling. Sublimation at 70°/0·1 mm. followed by crystallisation from light petroleum (b. p. 60—80°) gave *3-(α-ethoxypropionamido)butan-2-one* (0·66 g.) as prisms, m. p. 45° (Found : C, 57·3; H, 9·0; N, 7·4. $C_9H_{17}O_3N$ requires C, 57·7; H, 9·1; N, 7·5%).

α-Ethoxypropionamidoacetone.—α-Bromopropionamidoacetone (0·8 g.) in dry ethanol (10 c.c.) was added to a solution of sodium ethoxide, from sodium (0·11 g.) and ethanol (5 c.c.), and the solution left overnight at 15°. The reaction mixture, filtered from sodium bromide, was evaporated under reduced pressure to give a gum. Sublimation at 60°/0·5 mm. gave *α-ethoxypropionamidoacetone* (0·2 g.) as hygroscopic needles, m. p. 65° (Found : C, 55·4; H, 8·7; N, 8·3. $C_8H_{15}O_3N$ requires C, 55·5; H, 8·7; N, 8·1%).

ω-(α-Ethoxypropionamido)acetophenone.—ω-(α-Bromopropionamido)acetophenone (2·5 g.) in dry ethanol (15 c.c.) was treated with a solution of sodium ethoxide, from sodium (0·3 g.) and ethanol (5 c.c.). After 36 hours at 15° the ethanol was removed under reduced pressure and the residue extracted with boiling light petroleum (b. p. 100—120°; 10 × 10 c.c.). Concentration of the extract gave *ω-(α-ethoxypropionamido)acetophenone* (270 mg.) as needles, m. p. 89° (Found : C, 66·5; H, 7·4; N, 6·3. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2; N, 6·0%).

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THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, December 16th, 1949.*]

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185. *Stereochemistry of Metabolic Diols from Naphthalene and Anthracene.*

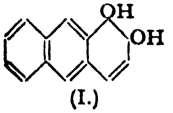
By J. W. COOK, J. D. LOUDON, and W. F. WILLIAMSON.

Resolution of *trans*-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-diol, through the *diesters* of *lævo*-menthoxyacetic acid, affords the *dextro-trans-* and *lævo-trans-*diols. The former of these is identical with the product obtained by hydrogenating the *lævo*-1 : 2-dihydronaphthalene-1 : 2-diol which was isolated by Young (*Biochem. J.*, 1947, **41**, 417) from the urine of rats dosed with naphthalene and which, accordingly, has the *trans*-structure.

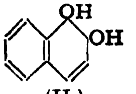
(±)-*cis-* and (±)-*trans*-1 : 2 : 3 : 4-Tetrahydroanthracene-1 : 2-diols have been synthesised and characterised. The properties of the (±)-*trans*-diol correspond with those described by Boyland and Levi (*ibid.*, 1935, **29**, 2679; cf. Booth and Boyland, *ibid.*, 1949, **44**, 361) for the hydrogenation product of the (±)-metabolite which is formed when anthracene is fed to rats or rabbits.

BOYLAND and LEVI (*Biochem. J.*, 1935, **29**, 2679) showed that anthracene, fed to rats and rabbits, is converted in part into lævorotatory and inactive forms, respectively, of the diol (I). Young (*loc. cit.*) isolated a lævorotatory form of the diol (II) from the urine of rats dosed with naphthalene. According to Booth and Boyland (*ibid.*, 1949, **44**, 361), the respective diols (I) and (II) are obtained in each case as a mixture of an optically active and an inactive form, the dextrorotatory predominating in the metabolites from rabbits, the lævorotatory in those from rats. Theoretically the diols can exist in *cis-* and *trans-*modifications and to each modification there will be *dextro-*, *lævo-*, and inactive forms. It is of interest in relation to the mechanism of biological oxidation to determine the stereochemical form(s) of these metabolites, and when the present investigation was begun the only guide was provided by the work of Boyland and

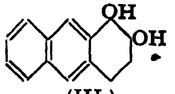
Shoppee (*J.*, 1947, 801), who inferred a *cis*-configuration for the metabolites (I) from the rapidity with which these diols were oxidised by lead tetra-acetate. Recently, however, in view of the negative response to Criegee's reagent for *cis*-diols (*viz.*, triacetylosmic acid, cf. Criegee, Marchand, and Wannowius, *Annalen*, 1942, **550**, 99), Booth and Boyland (*loc. cit.*) have preferred the *trans*-configuration for the anthracene metabolites and have supported the same configuration for the naphthalene metabolites by extensive evidence which in part anticipates our own.



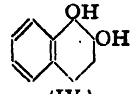
(I.)



(II.)



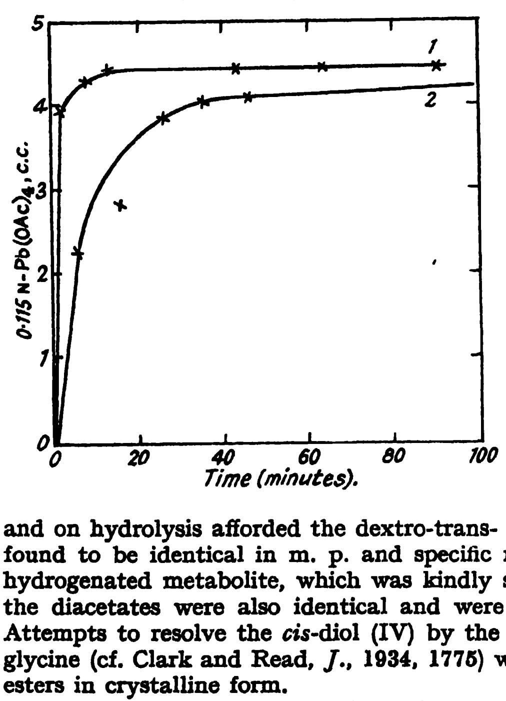
(III.)



(IV.)

The metabolites (I) and (II) are readily hydrogenated to the tetrahydro-diols (III) and (IV) respectively (Boyland and Levi, *loc. cit.*; Young, *loc. cit.*), and it was the aim of the present investigation to secure for reference and for optical resolution the *cis*- and *trans*-forms of these (±)-tetrahydro-diols. Straus and Rohrbacher (*Ber.*, 1921, **54**, 40) obtained the (±)-diol (IV) in *cis*- and *trans*-forms respectively by oxidation of 1 : 2-dihydronaphthalene with potassium permanganate and by stepwise hydrolysis of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydronaphthalene. These are satisfactory methods of preparation, and confirmation of the configurations assigned follows from (*a*) the results of applying to 1 : 2-dihydronaphthalene well-authenticated modern methods for *cis*- or *trans*-hydroxylation of a double bond (cf. Experimental), (*b*) tests with potassium triacetylosmate (cf. Experimental), and (*c*) the relative rates of oxidation by lead tetra-acetate determined by Criegee, Kraft, and Rank (*Annalen*, 1933, **507**, 159).

Oxidation of 1/4000 *mol. of* (1) cis- *and* (2) trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene with lead tetra-acetate.*



Resolution of *trans*-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-diol was effected through *diesters* produced by acylation with *lævo*-menthoxyacetyl chloride (cf. Wilson and Read, *J.*, 1935, 1269). The esters were separated by fractional crystallisation from light petroleum and on hydrolysis afforded the dextro-trans- and lævo-trans-*diols* (IV). The former diol was found to be identical in m. p. and specific rotation with a dextrorotatory specimen of the hydrogenated metabolite, which was kindly supplied by Professor L. Young: the m. p.s of the diacetates were also identical and were unaffected by admixture of the two samples. Attempts to resolve the *cis*-diol (IV) by the same means or through esters of *lævo*-menthylglycine (cf. Clark and Read, *J.*, 1934, 1775) were unsuccessful because of failure to obtain the esters in crystalline form.

For the synthesis of the *cis*- and *trans*-1 : 2 : 3 : 4-tetrahydroanthracene-1 : 2-diols (III), 2-anthrol was hydrogenated under pressure in the presence of copper chromite to an easily separable mixture of 9 : 10-dihydro- and 1 : 2 : 3 : 4-tetrahydro-2-anthrol. Von Braun and Bayer (*Annalen*, 1929, **472**, 105) reported the dehydration of the latter compound by distillation of the phenylurethane, but a more satisfactory method consists in heating the tetrahydroanthrol with fused potassium hydroxide. 1 : 2-Dihydroanthracene, so obtained, was converted, by treatment with osmium tetroxide in benzene–pyridine and subsequent hydrolysis of the ester complex, into the *cis*-diol (III), and the corresponding *trans*-diol was prepared (*a*) by hydrolysis of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydroanthracene *via* 1(or 2)-*bromo*-2(or 1)-*hydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene*, (*b*) together with some *cis*-diol, by oxidation of 1 : 2-dihydroanthracene with lead tetra-acetate.

The configuration assigned to these two diols is implicit in their respective methods of preparation and is confirmed by the fact that the isomer designated *cis*, alone of the pair, induces a colour change in the test with potassium triacetylosmate. Further confirmation is afforded by the relative rates of oxidation by lead tetra-acetate (see Fig.), the *cis*-isomer showing the expected higher rate. It will be observed that in each case oxidation of the diol corresponds to the consumption of one molar proportion of lead tetra-acetate, and in this respect there is correspondence with the data recorded by Boyland and Shoppee (*loc. cit.*) for oxidation of the *lævo*- and inactive metabolites (I). These authors are consequently in error in interpreting their results as showing the consumption of two moles of lead tetra-acetate with concurrent (or consecutive) oxidation of the diol grouping and of the *meso*-positions in (I). It is in any case clear that analogy between the *meso*-positions in anthracene and the corresponding positions in (I) is unsound.

Attempts to resolve the *cis*- and *trans*-diols (III) were unsuccessful, but the m. p.s of the synthesised (±)-*trans*-isomer and of the derived diacetate closely correspond with those reported by Boyland and Levi (*loc. cit.*) for the hydrogenated (±)-metabolite and its diacetate.

EXPERIMENTAL.

(±)-cis-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (IV).—(i) 1 : 2-Dihydronaphthalene (1 g.) (Bamberger and Lodter, *Ber.*, 1890, **23**, 208) was added to a solution of osmium tetroxide (2 g.) in dry ether (40 c.c.). After 7 days the solution was evaporated to dryness and the residue was refluxed for 3 hours with a solution of sodium sulphite heptahydrate (8 g.) in water (40 c.c.) and ethanol (20 c.c.). After filtration (hot) and removal of most of the alcohol, (±)-*cis*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (IV) was recovered in chloroform; it had m. p. 101° (from benzene) (Straus and Rohrbacher, *loc. cit.*, give m. p. 100—101°).

(ii) To 3·25 c.c. of a dried solution of hydrogen peroxide (5 c.c.; 90% by weight) in *tert.*-butyl alcohol (50 c.c.) were added, at 0°, 1 : 2-dihydronaphthalene (1 g.) and a solution of osmium tetroxide (0·1 g.) in *tert.*-butyl alcohol (10 c.c.). After 8 days at 0° the solution was concentrated under reduced pressure and the tarry residue was extracted with boiling water. The brown oil obtained by concentration of the aqueous extracts afforded, on recovery from benzene, the (±)-*cis*-diol (IV), m. p. 99—100°.

(±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—To a dried solution of hydrogen peroxide (0·5 g.) in *tert.*-butyl alcohol (2 c.c.) were added at 0° 1 : 2-dihydronaphthalene (2 g.) and a solution of selenium dioxide (0·06 g.) in *tert.*-butyl alcohol. After 8 days at 0° concentration afforded (±)-*trans*-diol (IV), m. p. 112° (from benzene) (Straus and Rohrbacher, *loc. cit.*, give m. p. 112—113°).

Criegee, Marchand, and Wannowius (*loc. cit.*, 1942) reported *trans*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (IV) to be exceptional (like *trans-cyclo*hexane-1 : 2-diol) in forming a diester with potassium triacetylosmate. Booth and Boyland (*loc. cit.*), without comment on this point, state that the reagent provides the usual distinction between these *cis*- and *trans*-diols. Re-examination showed that there is a marked difference in behaviour between the two forms: the *cis*-form gave immediately a rapid change from blue through green and red to brown, whereas with the *trans*-form no immediate change was perceptible, but after 30 minutes the blue had been replaced by a purple colour.

Resolution of (±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Attempts were first directed to the formation of a monoester (cf. Wilson and Read, *J.*, 1935, 1269) by the addition of freshly distilled (−)-menthoxyacetyl chloride (23·4 g., 1·4 mols.) (*Org. Synth.*, **23**, 52) to a cooled solution of the (±)-*trans*-diol (IV) (12·6 g., 1 mol.) in pyridine (100 c.c.). After 16 hours at room temperature the solution was poured into water, and an ethereal extract, thoroughly washed in turn with dilute hydrochloric acid, dilute sodium hydroxide, and water, and dried (Na_2SO_4), afforded a viscous oil which partly solidified when rubbed with light petroleum (b. p. 60—80°). This solid (24·5 g.), however, was found to contain unchanged diol and accordingly was treated as above with a further quantity of (−)-menthoxyacetyl chloride (29·9 g.; 1·8 mols.). The resulting solid (33 g.) was separated by fractional crystallisation from light petroleum (b. p. 60—80°) into a less soluble *diester* (A), m. p. 116—117°, $[\alpha]_D^{21}$ −21° (*c*, 1·0 in chloroform) (Found: C, 73·6; H, 9·2. $C_{34}H_{52}O_6$ requires C, 73·4; H, 9·3%), and a more soluble *diester* (B), m. p. 101—102°, $[\alpha]_D^{21}$ −170° (*c*, 1·0 in chloroform) (Found: C, 73·4; H, 9·3%). The nature of these compounds as diesters (not conclusively shown by analysis—calc. for $C_{22}H_{32}O_4$: C, 73·3; H, 8·9%) was supported by the observed consumption of 8·41 c.c. of 0·4095N-methanolic potassium hydroxide (≏ 2 moles) in hydrolysis of 0·9679 g. of ester (A). The diester (A) (8 g.) was heated under reflux for 3 hours with 2·5% methanolic potassium hydroxide (90 c.c.). Removal of the alcohol and recovery with ether afforded (−)-trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, m. p. 114—115° (from benzene), $[\alpha]_D^{21}$ −134° (*c*, 1·0 in chloroform) (Found: C, 73·4; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%). When a solution of the diol (213 mg.) in pyridine (4 c.c.) was treated at 0° with acetic anhydride (1 c.c.) and, after 12 hours, poured into ice and dilute sulphuric acid, the corresponding *diacetate*, m. p. 66—67° [from light petroleum (b. p. >120°)], was obtained: $[\alpha]_D^{21}$ +126° (*c*, 1·0 in chloroform) (Found: C, 67·8; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·4%). Similar treatment of the diester (B) afforded (+)-trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, m. p. 114—115° (from benzene), $[\alpha]_D^{21}$ +132° (*c*, 1·0 in chloroform), $[\alpha]_D^{21}$ +64° (*c*, 0·5 in ethanol), $[\alpha]_{5461}^{21}$ +44° (*c*, 0·5 in ethanol) (Found: C, 73·2; H, 7·1. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%), and its *diacetate*, m. p. 66—67° [from light petroleum (b. p. >120°)], $[\alpha]_D^{21}$ −125° (*c*, 1·0 in chloroform) (Found: C, 67·7; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·4%).

Young (*loc. cit.*) records for the (+)-hydrogenated metabolite (II) m. p. 115°, $[\alpha]_D^{25}$ +62° (*c*, 0·5 in ethanol), and a specimen kindly supplied by Professor Young did not depress the m. p. of (+)-*trans*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene and afforded a diacetate identical in micro-m. p. and mixed micro-m. p. with (−)-*trans*-1 : 2-diacetoxy-1 : 2 : 3 : 4-tetrahydronaphthalene.

1 : 2 : 3 : 4-*Tetrahydro-2-anthrol*.—2-Anthrol (10 g.) (Lagodzinski, *Annalen*, 1905, **342**, 68) in ethanol (100 c.c.) was hydrogenated in the presence of copper chromite (1 g.) at 200°/122 atm. for 7 hours. The crystalline solid, recovered from the filtered solution, was dissolved in ether and freed from 9 : 10-dihydro-

2-anthrol (m. p. 129°; cf. von Braun and Bayer, *loc. cit.*) by shaking the solution with 20% sodium hydroxide. 1 : 2 : 3 : 4-Tetrahydro-2-anthrol, recovered from the washed ethereal solution, had m. p. 142° (from ethanol) (Found : C, 85·1; H, 6·8 Calc. for $C_{14}H_{14}O$: C, 84·9; H, 7·1%) (von Braun and Bayer, *loc. cit.*, give m p. 148°).

1 : 2-*Dihydroanthracene*.—1 : 2 : 3 : 4-Tetrahydro-2-anthrol (4 g.) was heated for 1 hour with freshly fused potassium hydroxide (4 g.) at 180—210°. The product, recovered from ether, was sublimed at 100—120°/2 mm., and had m. p. 147—148° (from ethanol) (von Braun and Bayer, *loc. cit.*, record m. p. 150°) (Found : C, 93·4; H, 6·7. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%).

(±)-cis-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene* (III).—A solution of 1 : 2-dihydroanthracene (1·42 g.) in dry ether (10 c.c.) was added to a solution of osmium tetroxide (2 g.) in ether (100 c.c.) and pyridine (1·4 c.c.). After 16 hours the precipitate was collected and heated under reflux for 1 hour with a solution of sodium sulphite heptahydrate (8·1 g.) in water (40 c.c.) and ethanol (20 c.c.). After filtration (hot) and removal of most of the ethanol, the *diol* crystallised and had m. p. 133—135° (from benzene) (Found : C, 78·7; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). When a solution of the diol (125 mg.) in pyridine (2 c.c.) was treated at 0° with acetic anhydride (0·5 c.c.) and, after 12 hours at room temperature, was poured into iced water, the corresponding *diacetate*, m. p. 122° [from light petroleum (b. p. 60—80°)], was obtained (Found : C, 72·1; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%).

(±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene* (III).—(i) To a solution of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydroanthracene (2 g.) [m. p. 105—106° (from light petroleum, b. p. 60—80°); von Braun and Bayer, *loc. cit.*, record m. p. 102°] in acetone–water (4 : 1), kept at 50—60°, magnesium carbonate (1 g.) was added during 2·5 hours. The brown oil, obtained after filtration (hot) and removal of acetone, was extracted and dried in ether affording, on concentration, 1(or 2)-*bromo*-2(or 1)-*hydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene*, m. p. 102—103° [from light petroleum (b. p. 60—80°)] (Found : C, 60·6; H, 4·8. $C_{14}H_{13}OBr$ requires C, 60·6; H, 4·7%). This compound (0·5 g.) was heated under reflux for 1 hour with potassium hydroxide (0·15 g.) in water (10 c.c.). The *diol* recovered from ether had m. p. 162—163° (from benzene) (Found : C, 78·4; H, 6·8. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

(ii) 1 : 2-Dihydroanthracene (10 g.) was added to a solution of lead tetra-acetate (24 g.) in acetic acid (400 c.c.) and the mixture was heated at 80—90° for 1 hour. The cooled solution was poured into water, from which extraction with ether and recovery from the washed and dried ethereal extract gave an oil. This was hydrolysed by being heated under reflux (15 minutes) with potassium hydroxide (33 g.) in ethanol (500 c.c.). Subsequent dilution with water, removal of most of the ethanol, and recovery in ether afforded a mixture of *cis*- and *trans*-diols (III), which was separated by fractional crystallisation from benzene, the *trans*-form being the less soluble.

When a solution of the *trans*-diol (III) (118 mg.) in pyridine (2 c.c.) was treated with acetic anhydride (0·6 c.c.) and, after 12 hours at room temperature, was poured into iced water, the corresponding *diacetate*, m. p. 85—87° [from light petroleum (b. p. 60—80°)], was obtained (Found : C, 72·5; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). Hydrolysis of this diacetate regenerated the *trans*-diol, m. p. 162° [Boyland and Levi, *loc. cit.*, record m. p. 162° for the (±)-hydrogenated metabolite (II) and m. p. 84° for its diacetate].

Rate of Oxidation of cis- *and* trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene with Lead Tetra-acetate*.—To a solution of the diol (53 mg.) in acetic acid (10 c.c. distilled over chromium trioxide) kept at 18—19° by immersion in a thermostat, were rapidly added 10 c.c. of a standard solution of lead tetra-acetate, the time of addition being noted. At intervals, samples (1 c.c.) were withdrawn and run into a potassium iodide–sodium acetate buffer solution, and the liberated iodine was titrated against standard sodium thiosulphate. The results are given in the figure.

The *cis*-diol (III) produced an immediate change from blue to green; the *trans*-diol caused no change in the colour of potassium triacetylosmate.

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance (to W. F. W.) and to Professor Leslie Young for a sample of his reduced metabolite from naphthalene. Micro-analyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

University of Glasgow.

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186. *An Infra-red Spectroscopic Investigation of Double-bond Structure in Simple Acyclic Terpenes and Derivatives thereof.*

By D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard, and G. B. B. M. Sutherland.

The infra-red spectra of twenty-five purified acyclic monoterpene compounds are described and discussed with particular reference to the position and configuration of the double bonds. A semi-quantitative method for the infra-red detection of *iso*propenyl end-groups is outlined, and the present experimental results as well as those recorded by Thompson and Whiffen are interpreted on this basis. Very strong evidence is obtained that naturally occurring acyclic monoterpenes as a class possess the homogeneous *iso*propylidene end-group structure. In every purified sample examined by us, the proportion of the compound in the *iso*propenyl form never exceeded 3% and was usually very much less or possibly nil. Classical oxidative degradations afford indecisive conclusions in this field.

Some of the characteristic vibration frequencies of alcohol, ether, and vinyl groupings are shown to be modified if they occur in an allylic environment.

The nature of " geranyl chloride " as an anionotropic mixture of primary with some tertiary halide has been established by infra-red analysis of the partly resolved fractions resulting from low-pressure distillation.

A simple unresolved structural problem in organic chemistry is the question of the position of the double bond in the terminal *iso*propylidene (I) or *iso*propenyl (II) groups of acyclic monoterpenes and related substances (cf. Simonsen and Owen, " The Terpenes," Cambridge, 1947; *Endeavour*, 1949, **8**, 26). On oxidative degradation, such compounds generally behave as if they were mixtures of (I) with a smaller and variable proportion of (II), but there is other evidence suggesting that the terpenes are structurally homogeneous and that the ambiguous results of oxidation must be attributed to partial rearrangement. *E.g.*, Kuhn and Roth (*Ber.*, 1932, **65**, 1285) found that the ultra-violet absorption curves of the two crystalline *cis-trans*-isomeric dehydrogeranic acids (III) were incompatible with the presence of some 30% of the less highly conjugated *iso*propenyl form (IV) which is required by ozonolytic evidence (Cahn, Penfold, and Simonsen, *J.*, 1931, 3134; Kuhn and Roth, *loc. cit.*). Recent chemical work on the two crystalline *cis-trans*-isomeric geranamides (V; X = $CO{\cdot}NH_2$) (Caldwell and Jones, *J.*, 1946, 599), and the *X*-ray crystal-structure analysis of geranylamine hydrochloride (VI; X = NH_3Cl) (Jeffrey, *Proc. Roy. Soc.*, 1945, *A*, **183**, 388; cf. Sutton, *J.*, 1944, 306) also support the view that these crystalline acyclic terpene derivatives are homogeneous *iso*propylidene compounds, and that much of the older chemical work purporting to prove the presence of *iso*propenyl (II) as well as *iso*propylidene (I) end-groups is of doubtful value.

$CMe_2{:}CHR$ (I.)

$CH_2{:}CMe{\cdot}CH_2R$ (II.)

$CMe_2{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2H$ (III.)

$CH_2{:}CMe{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2H$ (IV.)

$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CHX$ (V.)

$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2X$ (VI.)

Quite generally, the use of oxidative degradation as an unequivocal method of detailed structure diagnosis has become increasingly suspect during recent years (see, *e.g.*, Clemo and Macdonald, *J.*, 1935, 1294; Karrer and Bretscher, *Helv. Chim. Acta*, 1943, **26**, 1758; Caldwell and Jones, *loc. cit.*; Young, McKinnis, Webb, and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 293). Accordingly, physical methods of structure analysis are desirable, and the present paper is the outcome of work initiated five years ago after a study of crystalline geranylamine hydrochloride. The methods and conclusions are set out in detail below. Very strong evidence has been obtained for the absence of *iso*propenyl end-groups (II) from the structure of simple acyclic terpenoid compounds. At the same time, useful information has become available about the allylic isomerism of the second double bond in molecules such as geranyl chloride and its derivatives.

Earlier Spectroscopic Work.—Unconjugated acyclic terpenes do not display characteristic high-intensity absorption in the range 2000—4000 A. (cf. Bateman and Koch, *J.*, 1944, 600). Little significance can therefore be attached to the work of Savard (*Bull. Soc. chim.*, 1929, [iv], **45**, 398) who examined citronellol, rhodinol, and geraniol in this spectral region where the low-intensity absorption is non-selective and excessively sensitive to traces of chromophoric impurities. On the other hand, Kuhn and Roth's interpretation of the high-intensity ultra-violet absorption curves of the fully conjugated dehydrogeranic acids (*loc. cit.*), based on measurements by Hausser and Smakula, appears to be sound. Ultra-violet spectroscopical analysis of the structure of terpenes is restricted to the few special cases where conjugation occurs, and even there the sensitivity of the method is relatively limited. The application of Raman spectroscopy was discussed and adversely criticised by Angus (*Indian Acad. Sci.*, Raman Jubilee Vol., 1935, 529); at that time instrumentation and physical accuracy were sometimes still imperfect, few if any pure standards were available, and the purity of the investigated terpene samples was not always rigorously controlled before and during irradiation, but the usefulness and reliability of Raman data have now been firmly established (cf. Fenske *et al.*, *Ind. Eng. Chem. Anal.*, 1947, **19**, 700; *Analyt. Chem.*, 1949, **21**, 12). At the same time, infra-red absorption probably offers advantages over the Raman method of vibrational spectroscopy in resolving the *iso*propenyl–*iso*propylidene controversy. As a result of an enquiry from Sir John Simonsen, Thompson and Whiffen (*J.*, 1948, 1412) thus examined various samples of acyclic terpenes and concluded that " in general, the compounds examined appear to be mixtures of the two forms containing terminal *iso*propenyl and *iso*propylidene groups " and that " the proportions of the two forms vary in different cases, but it may be significant that in the majority the *iso*propylidene type is predominant." No physical constants or other preparative details of their compounds were given, and the purity of some of their samples was known to be questionable. Thompson and Whiffen's conclusions must therefore be regarded as preliminary and the authors themselves were aware of this limitation in concluding their paper with the remarks: " It is evident that this problem might repay a more detailed study using a larger number of compounds, particular attention being paid to the origin or method of preparation, and to freedom from oxidation or impurities." With the aid of approximate extinction coefficients, it will be shown that both their and our results are in fact incompatible with the conclusion that most of the compounds contained *appreciable* amounts (15—50%) of *iso*propenyl end-groups as required by the evidence of oxidative degradation.

Physical Basis of the Present Analytical Method.—It has been amply established in recent years that the infra-red absorption spectra of olefinic hydrocarbon compounds are sharply differentiated according to the number and relative position (symmetrical or unsymmetrical, *cis* or *trans*) of one or more hydrogen atoms directly attached to the unsaturated carbon atoms (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246; Rasmussen and Brattain, *J. Chem. Physics*, 1947, **15**, 120, 131, 135; Kilpatrick and Pitzer, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 191; Sheppard and Sutherland, *J.*, 1947, 1540; *Proc. Roy. Soc.*, 1949, *A*, **196**, 195; Amer. Petroleum Inst., " Catalog of Infra-Red Spectrograms," 1949). The following *strong* bands due to out-of-plane deformational modes of vibration of the olefinic hydrogen atoms always occur at or near the frequencies indicated, whenever the requisite structural groupings are present (R = alkyl or substituted alkyl):

$CHR{:}CR'R''$	800—840 cm.$^{-1}$	$CH_2{:}CRR'$	890 cm.$^{-1}$
cis-$CHR{:}CHR'$	690 „	$CH_2{:}CHR$	910 and 990 cm.$^{-1}$
trans-$CHR{:}CHR'$	965 „		

No exception to these correlation rules has yet been found, although the A.P.I. catalogue alone lists some eighty unsaturated hydrocarbons. Failure to absorb at any of the given characteristic frequencies is therefore proof that the corresponding grouping is absent; in particular, the presence of *iso*propenyl groups may be safely discounted when no absorption occurs close to 890 cm.$^{-1}$ (at suitable path length). On the other hand, the appearance of bands at or near the given frequency positions does not necessarily indicate the presence of any of the above types of double bond, since other vibrations of the molecular framework often happen to give rise to absorption in this spectral region. For example, *n*-octane, 3-ethylhexane, 3-methyl-3-ethylpentane (A.P.I., *op. cit.*), and crystalline geranylamine hydrochloride (see below) display a marked absorption near 890 cm.$^{-1}$, although the $CH_2{:}CRR'$ grouping is certainly absent in these compounds. In many cases, the suspected presence of a given type of olefinic structure can be confirmed by reference to the C=C stretching frequency near 1660 cm.$^{-1}$ (Sheppard and Sutherland, *loc. cit.*, 1947; Thompson and Whiffen, *loc. cit.*); $CHR{:}CR'R''$ gives rise to an infra-red band near 1670 cm.$^{-1}$, but $CH_2{:}CRR'$ and $CH_2{:}CHR$ absorb around 1645 cm.$^{-1}$. Here again, however, some caution must be exercised in the assignment of weak bands which may occasionally represent overtones or combinations of lower frequencies; both *cis*- and *trans*-3-methylpent-2-ene, for instance, exhibit absorption between 1620 and 1660 cm.$^{-1}$, although they do not contain a terminal methylene group (A.P.I., *op. cit.*). The position may be summarised by stating that *the* absence *of a particular double-bond structure in a hydrocarbon residue can be inferred with complete confidence from the absence of the characteristic infra-red frequencies at suitable path length, whereas additional evidence is sometimes required to prove the* presence *of a suspected grouping.*

In order to estimate the composition of isomeric mixtures and to fix an upper analytical limit of detection for the infra-red method, we must know the molecular extinction coefficients of the characteristic olefinic bands. It has been pointed out elsewhere (Sheppard and Sutherland, *loc. cit.*, 1947) that both the characteristic hydrogen deformation and the bouble-bond stretching frequencies of $CH_2{:}CRR'$ (*e.g.*, *iso*propenyl) groupings exhibit relatively much greater absorption intensities than do the corresponding frequencies of $CHR{:}CR'R''$ (*e.g.*, *iso*propylidene) groups in the pure compounds. The sensitivity of the infra-red method of detecting the very strongly absorbing *iso*propenyl groups can be estimated from the approximate molar decadic extinction coefficients of a representative number of pure compounds which have now been determined in dilute solution and are listed in the table below.

Approximate infra-red extinction coefficients of iso*propenyl and* iso*propylidene groups.*

Compound.	Type.	Frequency (cm.$^{-1}$).	ε (litres.g.-mol.$^{-1}$ cm.$^{-1}$).
Geraniolene (mainly V; X = H)	*iso*Propenyl	890	120 (in CCl_4)
α-Lupene [1]	,,	885	150 ,,
Lupeol [2]	,,	883	200 (in CS_2)
2-Methylpent-1-en-4-one	,,	895 [3]	160 [3] ,,
2 : 3 : 3-Trimethylbut-1-ene	,,	890	155 (in CCl_4)
2 : 4 : 4-Trimethylpent-1-ene	,,	890	155 ,,
2-Methylpent-1-en-4-one	,,	1650 [3]	24 [3] ,,
2 : 3 : 3-Trimethylbut-1-ene	,,	1640	20 (in C_6H_{12})
2-Methylpent-2-ene	*iso*Propylidene	830	38 (in CS_2)
2-Methylbut-2-ene	,,	1680	$1 < ε < 10$ [4] (neat)

[1] A pentacyclic triterpene hydrocarbon, $C_{30}H_{50}$, of known structure (see Experimental).

[2] A pentacyclic triterpene alcohol, $C_{30}H_{50}O$, of known structure (see Experimental).

[3] Taken from A.P.I. spectrogram (*loc. cit.*, serial no. 634).

[4] Estimated from one single spectral run. According to Kletz and Sumner (*J.*, 1948, 1456), the extinction coefficient of the *iso*propylidene C=C stretching frequency band in 2 : 4 : 4-trimethylpent-2-ene is about 0·35 times that of the corresponding *iso*propenyl absorption in 2 : 4 : 4-trimethylpent-1-ene.

Clearly, the extinction coefficient of the 890-cm.$^{-1}$ band of the *iso*propenyl group is much greater than that of either of the two characteristic *iso*propylidene bands or the 1645-cm.$^{-1}$ C=C stretching frequency of the *iso*propenyl double bond. The relatively low value of ε observed in geraniolene can almost certainly be ascribed to the presence of structural isomers in this hydrocarbon (cf. Simonsen and Owen, *op. cit.*; Naylor, *J.*, 1947, 1532), and the anomalously high value obtained for lupeol may not be reliable owing to the use of a different cell in this case (see Experimental). Whether or not the 890-cm.$^{-1}$ band extinction coefficient of the *iso*propenyl group remains *strictly* constant in different compounds (cf. Thompson and Whiffen, *loc. cit.*; Anderson and Seyfried, *Analyt. Chem.*, 1948, **20**, 998), it is evidently always high, and quite small amounts of *iso*propenyl groups could not escape detection by the infra-red method. As little as 1% of the hypothetical *iso*propenyl form of a simple terpene, for instance, would give rise to about 10% absorption in a 0·05-mm. path-length of the isomeric mixture.

According to the evidence of chemical oxidations provided by Grignard and his school, most acyclic monoterpenes contain 15—50% of the *iso*propenyl isomer admixed with an excess of the *iso*propylidene form (see Simonsen and Owen, *op. cit.*). On the basis of the above extinction coefficients, more than 70% absorption should then be displayed at the 890-cm.$^{-1}$ band when the spectrum is examined through a conventional path-length of 0·05 mm. of the liquid monoterpene. In actual fact, however, the absorption generally appears to be at most 10% of this, both in our own purified samples and in those examined by Thompson and Whiffen (particularly their citronellol " B," geranamide, citral, linalool, and dihydromyrcene " A "). Contrary to first impressions, therefore, Thompson and Whiffen's published data also indicate that the chemical evidence is in many instances altogether unreliable, and that many of the acyclic terpenes are almost, if not completely, homogeneous *iso*propylidene structures.

EXPERIMENTAL.

Most of the infra-red spectra were measured with one of two Hilger D 209 spectrometers: one at Cambridge was employed under double-beam conditions (cf. Sheppard and Sutherland, *loc. cit.*, 1947), and the other at Welwyn was employed as a single-beam instrument in an exhaustively dried atmosphere (humidity below 5%). Interference by water-vapour absorption in the 1640—1670-cm.$^{-1}$ region was therefore rendered insignificant. The spectra of a few samples, and most of the extinction coefficients given in the above table, were determined on a Grubb–Parsons single-beam instrument as described elsewhere (Barnard, Fabian, and Koch, *J.*, 1949, 2442). The effective slit widths employed were 3—5 cm.$^{-1}$ at 890 cm.$^{-1}$, and 7—10 cm.$^{-1}$ at 1650 cm.$^{-1}$. A fixed absorption cell (within a very small tolerance 0·1 mm. thick) was used for all extinction measurements, except in the case of lupeol which was investigated in a 0·25-mm. cell at higher molar dilution. The liquid terpene samples were studied as films from

0·05 to 0·1 mm. thick between sodium chloride plates, and the crystalline samples in suspension in "Nujol" as well as in solution as indicated. The commercial samples of the various terpenes were purchased from Messrs. Boake Roberts & Co., except when otherwise specified. All liquid compounds were freshly distilled and either examined immediately or kept sealed *in vacuo* between distillation and spectrographic examination.

Compounds used for Extinction-coefficient Measurements.—The sample of geraniolene (mainly V; X = H) was that described by Dr. R. F. Naylor elsewhere (*loc. cit.*). α-Lupene and lupeol were pure crystalline samples given to us by Professor E. R. H. Jones (cf. Heilbron, Kennedy, and Spring, *J.*, 1938, 329; Jones and Meakins, *J.*, 1941, 757). Pure 2 : 3 : 3-trimethylbut-1-ene was prepared by Dr. J. L. Bolland by dehydration of 2 : 3 : 3-trimethylbutan-2-ol obtained from *tert.*-butylmagnesium chloride and acetone, and 2 : 4 : 4-trimethylpent-1-ene was a specially distilled sample obtained from Imperial Chemical Industries, Limited, through Dr. A. G. Evans. Dehydration of 2-methylpentan-2-ol with iodine afforded a mixture of 2-methylpent-2-ene with 2-methylpent-1-ene which gave the following fractions after distillation through a column packed with Dixon copper gauze (23 theoretical plates): (i) b. p. 64·3—66·0°/754 mm. (70 g.) (25% of 2-methylpent-1-ene); (ii) b. p. 66·0—66·4°/754 mm. (70 g.) (10% of 2-methylpent-1-ene); (iii) b. p. 66·5—66·6°/751 mm. (37 g.) (3% of 2-methylpent-1-ene); (iv) b. p. 66·6°/751 mm. (3·5 g.) (0·2% of 2-methylpent-1-ene). Fraction (iv) was used (the isomer contents in this preparation, which was made by Dr. J. I. Cunneen, were established by infra-red analysis). 2-Methylbut-2-ene was similarly prepared by Dr. A. W. Kenchington from 2-methylbutan-2-ol, and had $n_D^{15.5}$ 1·3908 (2-methylbut-1-ene content, 0·1%).

2-Methylhept-2-en-6-one (VII). A commercial sample from Messrs. Boake Roberts & Co. afforded a solid semicarbazone only with considerable difficulty, even after fractionation (boiling range 59—70°/12 mm; refractive index range $n_D^{11.5}$ 1·4562—1·4430). A similar sample from Messrs. Hopkin and Williams Ltd. distilled over a much smaller range (55—57°/12 mm.; $n_D^{11.5}$ 1·4625) and gave a good yield of solid semicarbazone from aqueous alcohol. The pure derivative was obtained in the form of colourless needles, m. p. 135·5—136° (lit., *ca.* 135°), after repeated crystallisation from benzene–light petroleum (b. p. 60—80°). Spectroscopically and otherwise identical ketone samples were obtained by regeneration from this semicarbazone by (*a*) steam-distillation with phthalic anhydride, or (*b*) prolonged cold treatment with 2N-sulphuric acid and light petroleum (b. p. 40—60°). Pure 2-methylhept-2-en-6-one has b. p. 58°/12 mm., $n_D^{12.5}$ 1·4414 (we are indebted to Mr. A. L. Morris for these preparations). Another specimen was obtained directly by alkaline cleavage of citral (commercial grade), followed by simple fractionation (b. p. 66—66·5°/16 mm.; n_D^{13} 1·4420); it exhibited a spectrum indistinguishable from that of the products obtained as above from the pure semicarbazone.

(±)-*2-Methylhept-2-en-6-ol* (VIII). The above ketone was reduced with aluminium *iso*propoxide in *iso*propyl alcohol to give the corresponding alcohol as a colourless, slightly viscous liquid, b. p. 76·5—77°/14 mm., $n_D^{11.5}$ 1·4515, n_D^{20} 1·4481.

Citronellol (3 : *7-dimethyloct*-6-*en*-1-*ol*) (IX). Commercial citronellol ("C" and "Q" grades) is a complex mixture. On fractionation through a 15-plate column under reduced pressure, "C" grade was found to consist largely of material possessing almost exactly the b. p. (113·8—114·2°/14 mm.) and refractive index (n_D^{21} 1·4561) attributed to pure citronellol (Simonsen and Owen, *op. cit.*). "Q" Grade appears to be more heterogeneous. After neglecting a small fore-run, the following fractions were collected in approximately equal proportions: (i) b. p. 109—112°/17 mm., n_D^{21} 1·4498; (ii) b. p. 112—113·5°/17 mm., n_D^{21} 1·4535; (iii) b. p. 113·5—115°/17 mm., n_D^{21} 1·4598; (iv) a dark residue, n_D^{21} 1·4680.

Rhodinol (IX). The main bulk of a commercial sample had b. p. 117—118°/20 mm., n_D^{20} 1·4660.

Citronellal (3 : *7-dimethyloct*-6-*en*-1-*al*) (X; X = O). Fractionation of the commercial product yielded a considerable amount of low-boiling material and a main fraction, b. p. 89·0—89·5/17 mm., n_D^{20} 1·4500.

Citronellal semicarbazone (X; X = $N{\cdot}NH{\cdot}CO{\cdot}NH_2$). This was prepared from the above purified aldehyde according to the directions of Tiemann and Schmidt (*Ber.*, 1897, **30**, 34) and had m. p. 82·5° [after three crystallisations from light petroleum (b. p. 60—80°)].

Geraniol (3 : *7-dimethylocta*-trans-2 : 6-*dien*-1-*ol*) (VI; X = OH). A commercial sample, purified *via* the calcium chloride adduct, had b. p. 114°/13 mm., n_D^{14} 1·4782. Another sample was specially prepared from the crystalline diphenylurethane (see below) which was decomposed in the usual manner, the last traces of admixed diphenylamine being removed chromatographically on alumina (geraniol was more strongly adsorbed). This specimen distilled at 110°/12 mm., and had n_D^{11} 1·4806 (free from diphenylamine according to the ultra-violet light absorption test). The two geraniol samples displayed identical infra-red spectra.

Nerol (3 : *7-dimethylocta*-cis-2 : 6-*dien*-1-*ol*) (VI; X = OH). This alcohol was prepared in a pure state by extensive fractional crystallisation of the diphenylurethane mixture obtained from a commerical sample after 2 treatments with excess of calcium chloride. The final diphenylurethane (see below) was decomposed in the usual manner, and the regenerated alcohol freed from diphenylamine (ultra-violet light absorption test) by distillation and chromatography on alumina. This sample had b. p. 105°/12 mm., n_D^{11} 1·4795 (tetrabromide, silky needles, m. p. 116—118°). Another specimen (n_D^{14} 1·4749), kindly given us by Messrs. CIBA Ltd. of Basle, and said to contain a small proportion of geraniol, exhibited similar infra-red absorption.

Diphenylurethanes of geraniol and nerol (VI; X = $O{\cdot}OC{\cdot}NPh_2$). These well-known derivatives (cf. Simonsen and Owen, *op. cit.*) formed a continuous series of mixed crystals of space group C. 2/c. We are indebted to Dr. G. A. Jeffrey for the following crystallographic data:

		Unit cell dimensions in A.				
Alcohol basis of derivative.	M. p.	[*a*].	[*b*].	[*c*].	β.	Vol. in A.^{3}.
Pure geraniol	80·5—81°	30·26	6·31	24·20	116·7°	4126
Mixture M	60—63	30·09	6·37	23·87	117·6	4055
Mixture N	52—55	30·01	6·44	23·67	118·4	4024
Pure nerol	50—51	29·96	6·50	23·55	119·0	4011

Geranamides I *and* II (trans- and cis-V; X = $\mathrm{CO{\cdot}NH_2}$). The preparation of these crystalline compounds is fully described elsewhere (Caldwell and Jones, *loc. cit.*; Barnard and Bateman, following paper).

Digeranyl (2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 6 : 10 : 14-*tetraene*) (XI) *and* iso*digeranyl* (XV) These are described elsewhere (Barnard and Bateman, following paper).

Digeranyl ether (XII) (b. p. 152°/0·1 mm., n_D^{20} 1·4846). This was prepared by Dr. R. F. Naylor (*J.*, 1949, 2724) by interaction of geranyl chloride with the potassium derivative of geraniol in ethereal solution.

Homogeranic acid (VI; X = $\mathrm{CO_2H}$) *and* iso*homogeranic acid* (XIV; X = $\mathrm{CO_2H}$). These and their respective amides are described elsewhere (Barnard and Bateman, following paper).

Geranylamine hydrochloride (1-*amino*-3 : 7-*dimethylocta*-trans-2 : 6-*diene hydrochloride*) (VI; X = $\mathrm{NH_3Cl}$). This compound, m. p. 146°, has been fully described by Sutton (*loc. cit.*) and Jeffrey (*loc. cit.*).

Linalool (3 : 7-*dimethylocta*-1 : 6-*dien*-3-*ol*) (XIV; X = OH). Two commercial samples of different botanical origin (Bois de Rose and Bergamot) yielded on fractionation an identical main constituent, b. p. 86°/14 mm., n_D^{19} 1·4630.

Geranyl chloride (VI and XIV; X = Cl). This was prepared from geraniol as described elsewhere (following paper). A liquid boiling over the range 45—70°/0·2 mm. constituted 90% of the total yield. This was fractionated through a 30-cm. Vigreux column and separated into the following four equal fractions (Calc. for $\mathrm{C_{10}H_{17}Cl}$: Cl, 20·56%): (i) b. p. 40—45°/0·2 mm., n_D^{20} 1·4710 (Found: Cl, 20·3%); (ii) b. p. 45—47·5°/0·2 mm., n_D^{20} 1·4738 (Found: Cl, 20·4%); (iii) b. p. 47·5—52°/0·2 mm., n_D^{20} 1·4777 (Found: Cl, 20·5%); (iv) b. p. 52—53°/0·2 mm., n_D^{20} 1·4797 (Found: Cl, 20·5%).

Results and Discussion.

The infra-red absorption curves of most of the compounds investigated are presented in the accompanying diagrams, and others are more briefly described in the course of the discussion. A summary of the observed group frequencies is also given in tabular form. In comparisons of spectroscopic estimates for the maximum percentage of *iso*propenyl groups with deductions from chemical work, the latter values have been taken from the review by Simonsen and Owen (*op. cit.*).

Group frequencies (cm.$^{-1}$).

(? signifies uncertain structural correlation; w, weak band; —, band absent. The usual $\mathrm{CH_2}$ and $\mathrm{CH_3}$ bands near 1450 and 1375 cm.$^{-1}$ are not shown.)

	Structure.	$\mathrm{CH_2{:}CR_2}$.		$\mathrm{CHR{:}CR_2}$.	$\mathrm{CH_2{:}CHR}$.	$\mathrm{CH_2}$.	C·O or C:O.
Methylheptenone	(VII)	—	—	810		735	1720
Methylheptenol	(VIII)	—		832, 1670	?908, ?990, ?1645 w	745	1120
Citronellol (rhodinol)	(IX)	?885 w,	?1645 w	830, 1670		738	1055
Citronellal ...	(X; X = O)	?900,	?1645	825, 1675		738	1720
Citronellal semicarbazone	(X; X = $\mathrm{N{\cdot}NH{\cdot}CO{\cdot}NH_2}$)	?900 w		840		740	
Geraniol	(VI; X = OH)	?888 w,	—	838, 1670		740	1010
Nerol	(VI; X = OH)	?888 w,	—	832, 1670		742	1010
Geranamides ($\mathrm{CS_2}$ solution)	(V; X = $\mathrm{CO{\cdot}NH_2}$)	?900 w,		820, 825		745, 750	
Dimethyloctadiene	(VI; X = H)	?888 w,	—	820, 1678		740	
Dihydromyrcene	(VI; X = H and XIII)	889, —	1650	820, 1678		740	
Geraniolene	(V; X = H)	891,	1654	821, 1680		745	
Digeranyl	(XI)	?885 w,	—	832, 1670		738	
Digeranyl ether	(XII)	?887 w,	—	830, 1668		745	~1080
Homogeranic acid	(VI; X = $\mathrm{CO_2H}$)	—		827		740	
Homogeranamide	(VI; X = $\mathrm{CO{\cdot}NH_2}$)	?888 w		825		742	
Geranylamine hydrochloride	(VI; X = $\mathrm{NH_3Cl}$)	?888		835, 1670		725	
Geranyl chloride	(VI; X = Cl)	?890 w		845, 1665		745	
	(XIV; X = Cl)	?900 w		830	925, 990, 1415, 1645	745	
Linalool	(XIV; X = OH)	—		835, 1672	925, 997, 1415, 1645	740	1115
*iso*Digeranyl	XV	?885 w		832, 1670	908, 998, 1415, 1642	742	
*iso*Homogeranamide	(XIV; X = $\mathrm{CO{\cdot}NH_2}$)	—		835	920, 1005	730	

$\mathrm{CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3}$
(VII.)

$\mathrm{CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_3}$
(VIII.)

$\mathrm{CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}OH}$
(IX.)

$\mathrm{CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH{:}X}$
(X.)

Analysis of iso*Propenyl Groups.*—Methylheptenone (VII) and methylheptenol (VIII) are important degradation products of citral and geraniol respectively, and may be regarded as based on a common end-group structure of many simple acyclic terpenes. The infra-red spectra (Fig. 1) of both these simple compounds showed absence of absorption at 890 cm.$^{-1}$, so that no more than a fractional percentage of *iso*propenyl groups could have been present in the samples examined (see Introduction, p. 917).

Two commercial samples of the simplest terpene alcohol, citronellol (IX), were rather impure, but one of them (" C " grade) furnished on distillation a main fraction possessing physical constants identical with those given for the pure carbinol by Simonsen and Owen (*op. cit.*). This purified material, similarly to Thompson and Whiffen's citronellol " B," exhibited (Fig. 1) a weak band at 885 cm.$^{-1}$, accompanied by slight absorption near 1645 cm.$^{-1}$, so that a trivial amount (approximately 2% as estimated from the 885-cm.$^{-1}$ absorption) of the isomer containing the terminal *iso*propenyl double band *may* have been present. It will be shown below, however, that even this low proportion of terminal double bonds (if real) probably originated in some foreign impurity. Chemical evidence suggests that some 18—28% of the citronellol molecules exist in the *iso*propenyl form. A nearly identical spectrum was displayed by rhodinol (citronellol from a different source); a distinct enhancement of the characteristic *iso*propylidene double-bond absorption was almost certainly due to the presence of a small amount of the more highly unsaturated geraniol.

A commercial sample of citronellal (X; X = O) gave a spectrum very similar to that recorded by Thompson and Whiffen. This is compatible with the presence of some 5% of *iso*propenylic isomer or extraneous impurity; oxidative degradation indicates an isomer content of 40%. More significantly, the pure crystalline semicarbazone of this aldehyde (X; X = $\mathrm{N{\cdot}NH{\cdot}CO{\cdot}NH_2}$) displayed (Fig. 1) less than 5% absorption between 860 and 910 cm.$^{-1}$ in a path-length affording 30% absorption at the characteristic 840-cm.$^{-1}$ band of the *iso*propylidene group; an approximate calculation on the basis of these figures shows that the semicarbazone contains even less of the *iso*propenyl form than is allowed by the spectrum of purified citronellol (*i.e.*, less than 2%). Far from being an inseparable mixture of appreciable amounts of both *iso*propenyl and *iso*propylidene isomers as may be deduced on chemical grounds (see Simonsen and Owen, *op. cit.*), citronellal semicarbazone evidently exists in the homogeneous *iso*propylidene form (cf. Harries, *Annalen*, 1915, **410**, 1).

Differing from Thompson and Whiffen, we found that geraniol (VI; X = OH), purified in the usual manner *via* its solid adduct with calcium chloride, displayed (Fig. 1) no absorption peak near 1645 cm.$^{-1}$, and only a small band at 890 cm.$^{-1}$ (less than 1% of *iso*propenyl form present). The stereoisomeric nerol, regenerated from the diphenylurethane derivative, was similar in this respect (see Fig. 1). Oxidative data suggest the presence of over 20% of the *iso*propenyl isomers in these alcohols. Infra-red analysis of various chemical derivatives of geraniol, nerol, and the corresponding aldehydes, citral *a* and *b*, also supports the conclusion that the original alcohols are free from *iso*propenyl groups. Thus both the solid and the solution spectra of the two stereoisomeric geranamides (V; X = $\mathrm{CO{\cdot}NH_2}$) (see Fig. 2) are incompatible with the presence of more than 3% of this structural grouping. The dimethyloctadiene (VI; X = H), obtained by sodium–liquid ammonia reduction of geraniol, cannot contain as much as 2% of the *iso*propenyl isomer according to the spectrum already reported (Sheppard and Sutherland, *loc. cit.*, 1947; Thompson and Whiffen, *loc. cit.*), and the synthetic " double molecule " digeranyl (XI) has now been found to display closely similar absorption (Fig. 3). Again, the intensity of the band at 887 cm.$^{-1}$ in the spectrum of synthetic digeranyl ether (XII) (see Fig. 3), if attributed to *iso*propenyl structures, limits their proportion to 3% of the total end-groups present.

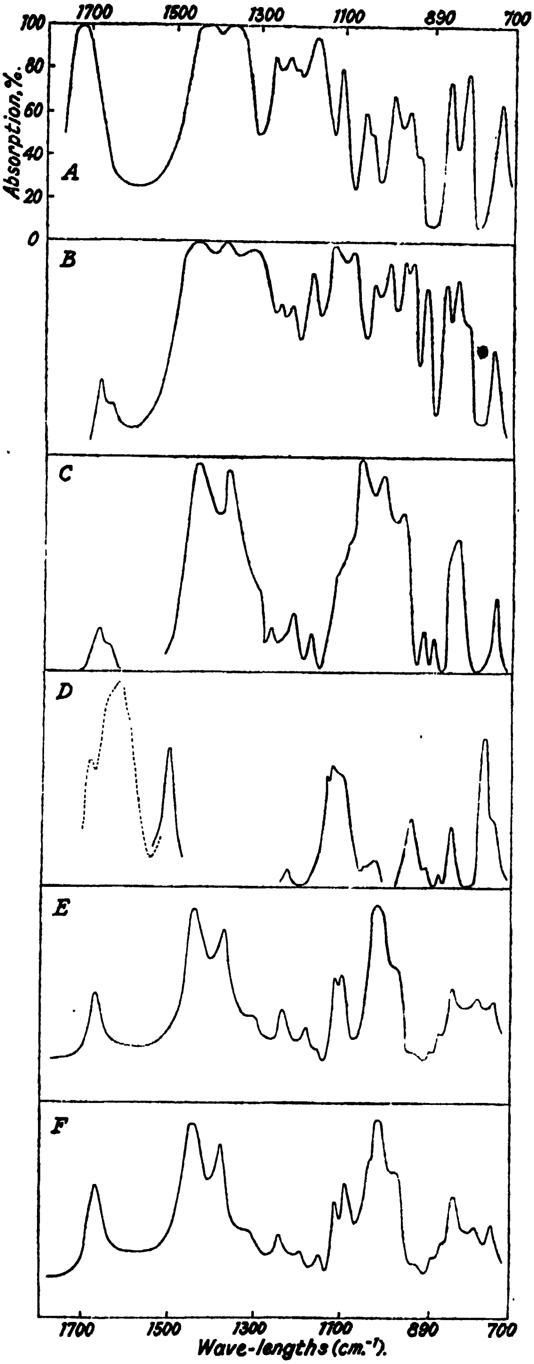
$\mathrm{(CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot})_2}$
(XI.)

$\mathrm{(CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot})_2O}$
(XII.)

Crystalline geranylamine hydrochloride (VI; X = $\mathrm{NH_3Cl}$) is notable in showing very strong absorption at 888 cm.$^{-1}$ (see Fig. 3) although the presence of the hypothetical *iso*propenyl isomer has been excluded by Jeffrey's (*loc. cit.*) complete *X*-ray structure analysis. The readily crystallised homogeranamide (VI; X = $\mathrm{CO{\cdot}NH_2}$) also exhibits a rather large band in this spectral region (see Fig. 2), but this again cannot be attributed to the presence of *iso*propenyl groups since the corresponding liquid acid (VI; X = $\mathrm{CO_2H}$) from which it was made showed no such absorption.

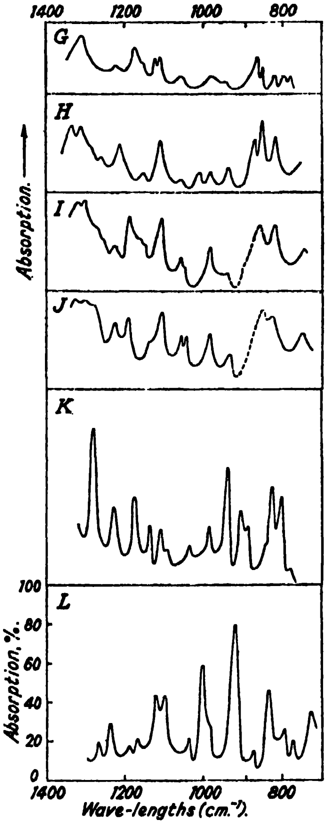
Elimination of the $\mathrm{-CH_2{\cdot}OH}$ grouping from geraniol results in the *iso*propenyl structure (V; X = H), which is the main constituent of geraniolene. The intense 890-cm.$^{-1}$ absorption

FIG. 1.



A, *Methylheptenone* (VII) (0·06-*mm. cell*). B, *Methylheptenol* (VIII) (0·06-*mm. cell*). C, *Citronellol* " *C* " (IX) (0·04-*mm. cell*). D, *Citronellal semicarbazone* (X; X = N·NH·CO·NH_2) (*in* " *Nujol* "). E, *Geraniol* (trans-VI; X = OH) (0·03-*mm. cell*). F, *Nerol* (cis-VI; X = OH) (0·03-*mm. cell*).

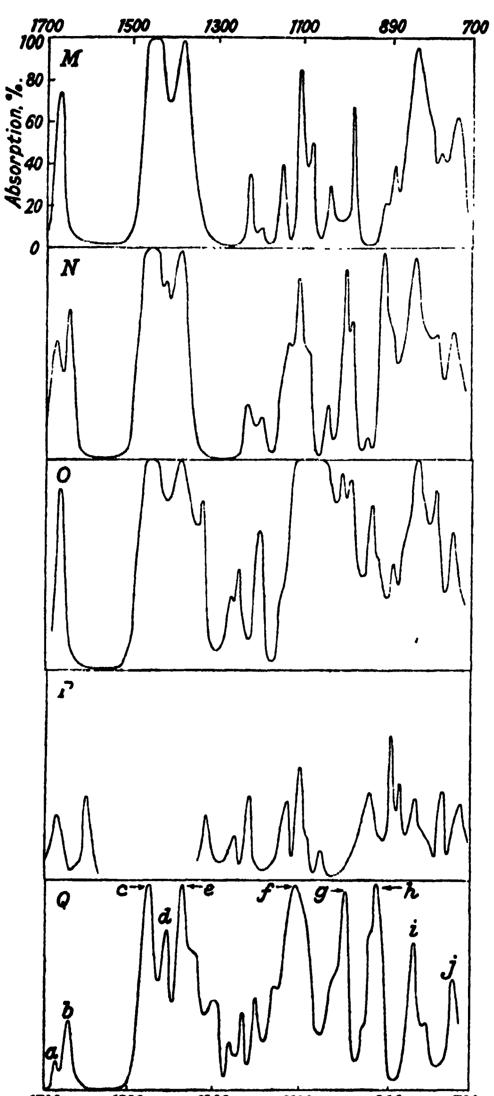
FIG. 2.



G, *Geranamide* I (trans-V; X = CO·NH_2) (*in* " *Nujol* "). H, *Geranamide* II (cis-V; X = CO·NH_2) (*in* " *Nujol* "). I, *Geranamide* I (20% *in* CS_2; 0·25-*mm. cell*). J, *Geranamide* II (20% *in* CS_2; 0·25-*mm. cell*). K, *Homogeranamide* (VI; X = CO·NH_2) (*solid*; 0·015 *mm. approx.*). L, iso*Homogeranamide* (XIV; X = CO·NH_2) (0·015-*mm. cell*).

of this hydrocarbon has already been referred to in the table of extinction coefficients (p. 917), as well as in the earlier paper by Sheppard and Sutherland (*loc. cit.*, 1947). A strong band at 890 cm.$^{-1}$ is also known to occur in the spectrum of " dihydromyrcene " obtained by sodium–ethanol reduction of natural myrcene (Sheppard and Sutherland, *loc. cit.*; Thompson and Whiffen, *loc. cit.*), where it arises from the presence of 2-methyl-6-ethylhepta-2 : 6-diene (XIII) (cf. Simonsen and Owen, *op. cit.*).

FIG. 3.



M, *Digeranyl* (XI) (0·1-*mm. cell*). N, iso*Digeranyl* (XV) (0·1-*mm. cell*). O, *Digeranyl ether* (XII) (0·1-*mm. cell*). P, *Geranylamine hydrochloride* (trans-VI ; X = NH_3Cl) (*in* " *Nujol* "). Q, *Linalool* (XIV ; X = OH) (0·04-*mm. cell*); a $>C{:}CH{\cdot}$; b $:CH_2$; *c* C–H; *d* $:CH_2$; *e* $\cdot CH_3$; *f* $\geqslant C{\cdot}OH$; *g* and *h* $\cdot CH{:}CH_2$; *i* $>C{:}CH{\cdot}$; *j* $\cdot C{\cdot}C{\cdot}C{\cdot}C{\cdot}C$.

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CEt{:}CH_2$$
(XIII).

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeX{\cdot}CH{:}CH_2$$
(XIV.)

Finally, we have failed to detect any sign of 890-cm.$^{-1}$ absorption in samples of linalool (XIV; X = OH) from two different natural sources (see Fig. 3) (cf. also Thompson and Whiffen), so that this terpene alcohol is unquestionably more than 99% homogeneous in the *iso*propylidene form.

It is clear from the above approximately quantitative infra-red characterisation of purified samples of methylheptenone, methylheptenol, citronellol, citronellal semicarbazone, geraniol, nerol, linalool, the two stereoisomeric geranamides, and certain other synthetic derivatives of geraniol, that none of these substances could possibly contain more than 2—3% of the hypothetical *iso*propenyl isomers, and some of them certainly contain considerably less. Much of the older chemical evidence indicating the presence of 15—50% of such isomers must therefore be deemed unreliable. Furthermore, since certain authentic non-*iso*propenyl compounds display absorption in the 890-cm.$^{-1}$ spectral region, it would seem reasonable to extrapolate most of the observed maximum permissible isomer percentages to zero, and to conclude that *iso*propenyl end-groups do not occur at all in natural acyclic monoterpenes but are confined to the cyclic series (*e.g.*, limonene) where the different structural conditions can reasonably be expected to stabilise the *iso*propenyl relative to the *iso*propylidene forms.

Analytical Significance of Chemical Purification.—During the preparation or isolation of terpenoid substances for infra-red analysis of the *iso*propenyl isomer content, two interrelated problems arise and will be considered in this section: how far the presence of terminal double-bond absorption at 890 and 1645 cm.$^{-1}$ may be attributed to a foreign impurity other than the *iso*propenylic isomer to be detected; and how far on the other hand the isomer in question may escape detection owing to its previous removal as an " impurity " during a rigorous purification.

Experience with such relatively low-boiling *iso*propylidene–*iso*propenyl mixtures as that of 2-methylpent-2-ene with 2-methylpent-1-ene (see Experimental) shows that even with the use of modern packed laboratory fractionating columns it would be extremely difficult to achieve effective separation of terpenoid isomers of this type in a single distillation. Except for citronellol, all terpene samples for infra-red examination were distilled in ordinary Vigreux or spiral columns, and hence there can be no question of the possible removal of *iso*propenyl forms during distillation. In particular, the methylheptenone obtained directly by alkaline cleavage of commercial citral followed by simple fractionation through a short Vigreux column proved constant-boiling and spectroscopically identical with a special sample regenerated from the pure crystalline semicarbazone. The reported homogeneity of this ketone must therefore refer to the entire bulk of the material prepared from natural sources, and not only to some chemically isolated fraction of it. The same conclusion applies to our samples of linalool which had been ordinarily distilled without passing through a crystalline derivative, and also to geraniol isolated from the calcium chloride adduct; the spectrum of the latter alcohol was identical with that of a special sample regenerated from the crystalline diphenylurethane. The same calcium chloride method had been used in the purification of the geraniol which behaves on oxidation as if it contained some 20% of the *iso*propenyl isomer. Similarly, it is the crystalline citronellal semicarbazone of sharp melting point identical with that of our own homogeneous sample which affords ambiguous results by chemical degradation. There can be no doubt, therefore, that the samples investigated by us are truly representative of the compounds described in the chemical literature.

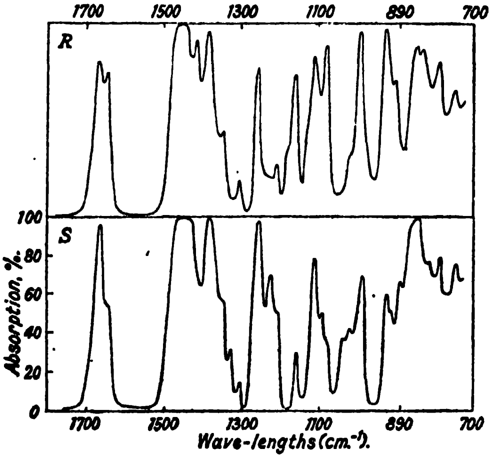
As already indicated, some trouble was experienced in obtaining reasonably pure specimens of citronellol from commercial sources; similar difficulties were evidently encountered by Thompson and Whiffen who have published spectrograms for two different grades of citronellol revealing different absorption intensities at the 890- and 1645-cm.$^{-1}$ bands. In view of the rather wide boiling and refractive index range of our crude samples (which also displayed somewhat strong absorption at these characteristic frequencies), we believe foreign impurities possessing terminal double bonds rather than the *iso*propenyl isomer of citronellol to have been present. The main citronellol fraction selected as a representative sample of the pure compound had very low terminal double-bond absorption and physical constants identical with those given for pure citronellol by Simonsen and Owen (*op. cit.*).

In their specimens of dimethyloctadiene (VI; X = H) obtained by the sodium–liquid ammonia reduction of geraniol, Thompson and Whiffen suspected the presence of an impurity containing vinyl groups, $CHR{:}CH_2$, because variable infra-red absorption occurred at 910, 990, and 1645 cm.$^{-1}$. In our own pure samples of this hydrocarbon (cf. Sheppard and Sutherland, *loc. cit.*, 1947), 910-cm.$^{-1}$ absorption was always small, and there was never any sign of 1645-cm.$^{-1}$ absorption which would be required by the presence of either vinyl or *iso*propenyl groupings. We see no reason to doubt, therefore, that chemically pure dimethyloctadiene from geraniol is a structurally homogeneous compound; on the other hand, it is possible and indeed probable that vinyl groups may be formed on autoxidation, which may account for the variable 910-cm.$^{-1}$ band intensities reported by Thompson and Whiffen.

Terpenoid Compounds containing Vinyl Groups.—The spectra of all the substances hitherto described exhibit certain common characteristic frequencies due to the presence of methyl (1370—1380 cm.$^{-1}$), saturated methylene (1450 and 735—745 cm.$^{-1}$), and *iso*propylidene or other $CHR{:}CR'R''$ (825—845 and 1665—1675 cm.$^{-1}$) groupings. Additional strong bands at 925, 997, 1415, and 1645 cm.$^{-1}$ arise in the spectrum of linalool (XIV; X = OH) (Fig. 3) where a vinyl group is present. The particularly intense 925- and 997-cm.$^{-1}$ absorptions obviously represent the out-of-plane vinyl C–H deformation frequencies which are normally found nearer 910 and 990 cm.$^{-1}$ in hydrocarbons. We have been able to observe similar band displacements in a variety of other allylic functional derivatives of vinyl hydrocarbons (see also below). As a general rule, in a molecule $CH_2{:}CH{\cdot}CRR'X$, where R may be either hydrogen or alkyl, but X represents a functional group, the 908—913-cm.$^{-1}$ hydrocarbon frequency is increased to 918—930 cm.$^{-1}$ (cf. Thompson and Torkington, *Trans. Faraday Soc.*, 1946, **42**, 432; Bateman *et al.*, *J.*, 1950, 936), whereas the 990-cm.$^{-1}$ frequency remains more or less constant when R = R′ = H, but is increased to 995—1005 cm.$^{-1}$, even in hydrocarbons (X = R), when the saturated carbon atom is fully substituted. The latter effect may be explained in terms of increased electron density at the nearer vinyl carbon atom resulting from the extensive substitution (cf. Sheppard and Sutherland, *loc. cit.*, 1949), but the reason for the marked shift in the 910-cm.$^{-1}$ frequency is not at present understood. The 1415- and 1645-cm.$^{-1}$ bands in the linalool spectrum are normal characteristic frequencies of vinyl groups in hydrocarbons, being associated respectively with an in-plane deformation of the terminal methylene group and the stretching of the double bond.

When the hydroxyl group of linalool or geraniol is replaced by halogen, the same halide is formed which is not constant-boiling (cf. Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 499; Sutton, *loc. cit.*) and has frequently been suspected of consisting of an anionotropic mixture of (VI) and (XIV; X = Hal) (cf., *e.g.*, Karrer and Helfenstein, *Helv. Chim. Acta*, 1930, **14**, 78), although positive proof of structure has never been obtained. These compounds are generally referred to simply as " geranyl " halides. In view of the practical and theoretical interest of the structural problem, we have carried out a careful low-pressure fractional distillation (bath temperature <70°) of freshly prepared geranyl chloride and subjected the resulting four fractions to immediate infra-red analysis. The experiment clearly shows that geranyl chloride as originally obtained is mainly (VI), with a small proportion of the lower-boiling tertiary form (XIV). Allylic chlorides of this type exemplify those moderately mobile anionotropic systems in which the isomeric constitution of the isolated product is governed both by the nature of the reaction introducing the mobile atom or group and by the facility of isomeric interconvertibility under the conditions of reaction and isolation (Catchpole, Hughes, and Ingold, *J.*, 1948, 8). Comparison with simpler allylic halides (*loc. cit.*) indicates that the linaloyl isomer occurs in ordinarily isolated " geranyl chloride " to considerably greater extent than its thermodynamic equilibrium proportion (*ca.* 1%), and in agreement with this fact prolonged heating at a moderate temperature (*ca.* 60°) gives a more homogeneous product.

FIG. 4.



R, *Geranyl chloride* (*first fraction*) (VI *and* XIV; X = Cl) (0·1 *mm. cell*). S, *Geranyl chloride* (*last fraction*) (VI *and* XIV; X = Cl) (0·1 *mm. cell*).

The spectra (Fig. 4) of the first and last fractions from the distillation of geranyl chloride are recorded in the figures. The highest-boiling fraction consists essentially of the primary chloride (VI), with strong absorption at 845 and 1665 cm.$^{-1}$, but the small band at 925 cm.$^{-1}$ and the shoulder at 1645 cm.$^{-1}$ indicate the presence of traces of tertiary chloride incorporating a vinyl group in the molecule. In the successively lower-boiling fractions, the 845- and 1665-cm.$^{-1}$-band strengths become gradually reduced, whereas the 925- and 1645-cm.$^{-1}$ bands are greatly intensified; at the same time, existing strong absorption at 988 cm.$^{-1}$ acquires additional intensity, and a new peak appears at 1415 cm.$^{-1}$. The interpretation of these changes in terms of increasing relative amounts of tertiary chloride incorporating the vinyl group is obvious. Other intensity changes occur simultaneously with those of the characteristic bands; in particular, the primary geranyl form appears to be associated with very intense absorption at 1255 cm.$^{-1}$, and the tertiary linaloyl form with a similarly strong band at 1080 cm.$^{-1}$. In view of the markedly different extinction coefficients of vinyl and trialkyl-substituted types of double bond, the spectrum of the lowest-boiling fraction indicates that even here the higher-boiling geranyl form predominates. It may be noted that the usual 910-cm.$^{-1}$ frequency of the vinyl group is again displaced to 925 cm.$^{-1}$; in allyl chloride itself, we observed the characteristic vinyl frequencies at 930, 985, 1415, and 1645 cm.$^{-1}$.

Two structurally isomeric hydrocarbons are produced during the coupling reaction of geranyl chloride over magnesium (Barnard and Bateman, *J.*, 1950, 932). The straight-chain digeranyl (XI) (with a very small band at 908 cm.$^{-1}$ probably due to a trace of the isomer) has already been referred to above; the structure of the branched-chain *iso*digeranyl (XV) is clearly characterised by intense vinyl absorption peaks at 908, 998, and 1642 cm.$^{-1}$, as well as a smaller

$$\mathrm{CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(CH{:}CH_2){\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CMe_2}$$

(XV.)

band at 1415 cm.$^{-1}$ (Fig. 3). The slight but significant increase in the usual 990-cm.$^{-1}$ frequency of the vinyl group to 998 cm.$^{-1}$ in this hydrocarbon can probably be attributed to the inductive effect of the three alkyl substituents at the adjacent carbon atom, as suggested above. *iso*Homogeranamide (XIV; X = $\mathrm{CO{\cdot}NH_2}$) similarly displays vinyl absorption at the displaced frequencies of 920 and 1005 cm.$^{-1}$ (Fig. 2).

Stereoisomerism.—In accordance with certain chemical evidence (Simonsen and Owen, *op. cit.*) and the known structure of the derived amine hydrochloride (Jeffrey, *loc. cit.*), geraniol (VI; X = OH) is believed to be the *trans*-isomer * with respect to the ambiguous configuration of the double bond adjacent to the primary alcohol grouping. The stereoisomeric nerol (*cis*-VI; X = OH) shows only minor differences of infra-red absorption, as might be expected from the general similarity of the two structures. The same kind of *cis-trans*-isomerism about a trisubstituted ethylenic linkage exists in the two 3-methylpent-2-enes where, again, relatively little, but nevertheless distinct, differentiation of infra-red spectra has been reported (A.P.I., *op. cit.*). We have also observed slight differences of infra-red absorption between the two isomorphous crystalline diphenylurethanes of geraniol and nerol. The *cis-trans*-isomeric geranamides (V; X = $\mathrm{CO{\cdot}NH_2}$) were crystallographically distinct from each other (Dr. G. A. Jeffrey, private communication) and the accompanying diagrams show that their infra-red spectra were more highly differentiated for the crystalline substances than they were for solution.

C–O *Frequencies of Terpenoid Alcohols.*—It appears to be generally true that saturated primary, secondary, and tertiary aliphatic alcohols display intense absorption at 1040—1080, 1100—1130, and 1160—1200 cm.$^{-1}$ respectively (cf. A.P.I., *op. cit.*; Sexton and Britton, *J. Amer. Chem. Soc.*, 1948, **70**, 3606), arising from the stretching vibration involving the C–O bond. The strong bands of the primary citronellol (IX) at 1055 cm.$^{-1}$ and of the secondary methylheptenol (VIII) at 1120 cm.$^{-1}$ are in line with this classification, but the characteristic frequencies of the allylic alcohols geraniol and nerol (VI; X = OH) at 1010 and of linalool (XIV; X = OH) at 1115 cm.$^{-1}$ are below the range assigned to their primary or tertiary class. Since allyl alcohol itself exhibits a similar shift of the alcohol band to 1027 cm.$^{-1}$ (Thompson and Torkington, *loc. cit.*, 1946), these low-frequency displacements appear to arise from the presence of the double bond in the allyl position and may be associated with a lowering of the force constant of the C–O bond in allylic environment. The characteristic ether absorption of digeranyl ether (XII) near 1080 cm.$^{-1}$ likewise occurs below that commonly observed above 1100 cm.$^{-1}$ in saturated primary ethers, and the displacement may again be ascribed to an allylic structural effect (for comparative data, cf. Barnes *et al.*, *Ind. Eng. Chem. Anal.*, 1943, **15**, 659).

The infra-red measurements were initiated at Cambridge, later continued by courtesy of the Directors at the Research Department of Messrs. Imperial Chemical Industries, Ltd. (Plastics Division), where facilities were kindly provided by Mr. H. A. Willis, and finally completed at the B.R.P.R.A. laboratories with valuable assistance from Miss J. M. Fabian. The work described forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association.

(D. B., L. B., AND H. P. K.) BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
48 TEWIN ROAD, WELWYN GARDEN CITY, HERTS.
(A. J. H., N. S., AND G. B. B. M. S.) LABORATORY OF COLLOID SCIENCE,
CAMBRIDGE.

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* We have adopted the general convention recently recommended by the Nomenclature Committee of the American Chemical Society (*Chem. Eng. News*, 1949, **27**, 1303), according to which geraniol is derived from *trans*-octadiene and should therefore be correctly formulated as 3 : 7-dimethylocta-*trans*-2 : 6-dien-1-ol. This convention seems both logical and in harmony with the universal practice of describing the two stereoisomeric polyisoprenes rubber and gutta-percha as *cis*- and *trans*-isomers respectively. Unfortunately, some confusion exists in the literature as many authors (*e.g.*, Simonsen and Owen, *op. cit.*; Caldwell and Jones, *loc. cit.*) have rather arbitrarily referred to geraniol and its derivatives as *cis*-isomers.

187. *Experiments relating to the Synthesis of Homogeranic Acid.*

By D. Barnard and L. Bateman.

Homogeranic acid (I; X = CO_2H) is obtained only in poor yield from *geranoyl chloride* by the Arndt–Eistert synthesis, and the production of the corresponding *cyanide* from geranyl chloride and cuprous cyanide is similarly inefficient. However, a novel and general method for synthesising allylic cyanides, *viz.*, allyl halide ⟶ allylmalonic ester ⟶ α-oximinoallylacetic acid ⟶ allyl cyanide, renders geranyl cyanide, and thence homogeranic acid, readily accessible. 1- and 3-Methylallyl cyanide and the hitherto difficultly obtainable cinnamyl cyanide have been prepared from the respective chlorides by the above method. The product from the condensation of 1-methylallyl chloride with sodiomalonic ester contains a small proportion of *3-methylallylmalonic* ester; the relation of this finding to the S_N2' mechanism of allylic halide replacement (Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185) is discussed.

Although no previous attempt to apply the Arndt–Eistert process

$$R{\cdot}CO_2H \longrightarrow R{\cdot}COCl \longrightarrow R{\cdot}CO{\cdot}CHN_2 \longrightarrow R{\cdot}CH_2{\cdot}CO_2H$$

to aliphatic αβ-unsaturated acids is on record, the successful conversion of several aromatic acids into substituted acetic acids and of an alicyclic βγ-unsaturated acid into the corresponding γδ-unsaturated acid by this method ("Organic Reactions", Wiley and Sons, N.Y., 1942, Vol. I, pp. 38 *et seq.*) gave reason to believe that the synthesis of homogeranic acid (I; X = CO_2H) from geranic acid (II; X = OH) could be realised without difficulty.

The first intermediate, *geranoyl chloride* (II; X = Cl), has not been described hitherto, but is readily prepared in good yield from the acid and thionyl chloride in the presence of pyridine, if particular care is exercised in purifying the thionyl chloride. Interaction of (II; X = Cl) with aqueous ammonia yields a geranamide (II; X = NH_2) mixture separable by fractional elution from alumina into two crystalline isomers. These are the compounds designated as geranamide-I and geranamide-II, respectively, by Caldwell and Jones (*J.*, 1946, 599), who first isolated them as rearrangement products from the action of Raney nickel on citral oxime. Comment on the structure of the compounds in the light of their infra-red spectra is made elsewhere (Barnard *et al.*, preceding paper). Notwithstanding the distinct preparative routes, the isolated mixtures contained the same relative proportion of isomers (5 : 1).

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2X \quad (I.) \qquad CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO{\cdot}X \quad (II.)$$

$$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeX{\cdot}CH{:}CH_2 \quad (III.)$$

The second stage of the projected synthesis also proceeds normally, to yield the liquid *diazomethyl* 2 : 6-*dimethylhepta*-1 : 5-*dienyl ketone* (II; X = CHN_2). The final stage, however, proved decidedly abnormal. Repeated attempts to rearrange the diazo-ketone to homogeranic acid (I; X = CO_2H) or to homogeranamide (I; X = $CO{\cdot}NH_2$) under the usual conditions using colloidal silver as catalyst gave only tar and much residual diazo-ketone. The possible catalytic activity of a variety of metallic compounds was then investigated. Although auric chloride proved to be an active catalyst for promoting the decomposition of the diazo-ketone in ethanol at room temperature, complex side-reactions greatly preponderated and, on hydrolysis, only 7% of *homogeranic acid* (I; X = CO_2H) was obtained.

Diazomethyl 2 : 6-dimethylhepta-1 : 5-dienyl ketone clearly possesses unusual stability, as is further emphasised by the fact that it can be distilled without appreciable decomposition at 0·05 mm. pressure from a bath at 100° (b. p. 87—88°). Although many diazo-ketones possess comparable thermal stability, few are resistant to the usual rearrangement procedures. The several indefinite interpretations of the mechanism of the rearrangement that have been propounded certainly offer no indication of any special function of the alkenyl substituent in the present example.

The limited success achieved forced our attention to preparative methods based on geranyl chloride. An inherent disadvantage of this approach is the possibility of allylic isomerism. This complication intrudes in three ways: (i) possible inhomogeneity of the terpenoid starting material or of an intermediate; (ii) similar inhomogeneity of the desired product even if its precursor were pure; and (iii) the analytical problem of identifying and characterising various isomers. The last of these, clearly of dominant importance, is now greatly facilitated by recent developments in the recording and interpretation of infra-red spectra (see Barnard *et al.*, *loc. cit.*).

Pure geraniol is entirely the primary allylic alcohol (I; X = OH). On treating it with thionyl chloride and pyridine (Forster and Cardwell, *J.*, 1913, 1341), a product boiling over a range of about 20° is obtained (cf. Ruzicka, *Helv. Chim. Acta*, 1923, 6, 492; Sutton, *J.*, 1944, 306), which gives analyses correct for the derived chloride and which infra-red spectroscopic analysis reveals to be a mixture of the primary (geranyl) (I; X = Cl) and the tertiary (linaloyl) (III; X = Cl) chloride in the ratio of roughly 5 to 1.* Separation of the isomers by fractionation is extremely difficult because of decomposition during the prolonged heating at the relatively high temperature needed. More rapid distillation at the lowest convenient pressure (*ca.* 0·2 mm.) effects some separation, the tail portions consisting of almost pure primary chloride. However, for reasons which will emerge, the use of the pure isomers offers no advantage in the present work.

Recent work by Lane, Fentress, and Sherwood (*J. Amer. Chem. Soc.*, 1944, 66, 545) indicated that the conversion of an allylic halide into the carboxylic acid homologue *via* the nitrile offered not only the most direct, but a most favourable structural, route to homogeranic acid. These authors showed that the simpler analogues of the constituents of the geranyl chloride mixture, *viz.*, 1- and 3-methylallyl chloride, interact with cuprous cyanide so that, independently of the nature of the pure halide or of the composition of an isomeric mixture, the same equilibrium mixture of cyanides is formed (91·5% of crotyl, 8·5% of 1-methylallyl). Furthermore, when the mixture is hydrolysed by acid, the 1-methylallyl constituent behaves abnormally and the isolated acid is derived solely from the crotyl isomer. Once again, however, the extension to di-isoprenic derivatives of a method successful with simpler analogues was disappointing. Under the experimental conditions of Lane *et al.* (*loc. cit.*) and modifications thereof, the maximum yield of *geranyl cyanide* was no more than 11%, in marked contrast to the approximately 90% conversion obtained in the methylallyl system. As expected, isomeric heterogeneity of the product was indicated by a boiling range of 7° (cf. geranyl chloride), but in addition it appeared to be very slightly impure. Although this synthesis is therefore of little preparative value in the geranyl series, the present work corroborates the American authors' important findings concerning the formation of homogeneous hydrolytic products from isomeric mixtures of allylic nitriles. Alkaline hydrolysis converted the above geranyl cyanide into homogeneous homogeranic acid (I; X = CO_2H), which in turn has been converted *via* its *acid chloride* into crystalline *homogeranamide*, identical in melting point and infra-red spectrum with a specimen prepared from homogeranic acid isolated from the rearrangement of diazomethyl 2 : 6-dimethylhepta-1 : 5-dienyl ketone. A similarly identical specimen is obtained directly from the cyanide on mild hydrolysis with alkaline hydrogen peroxide, thus establishing that no double-bond displacement occurs during the relatively severe hydrolysis of the cyanide. The ultra-violet absorption spectrum also proves the absence of αβ-unsaturated conjugation in the acid.

At this stage, when the possibility of finding an improved route to homogeranic acid seemed remote—especially as we had found in the meantime that carboxylation of geranylmagnesium chloride yields the tertiary allylic derivative (III; X = CO_2H) (see following paper)—Barry and Hartung (*J. Org. Chem.*, 1947, 12, 460) described preparations of α-oximino-acids. One method involves a novel transformation of alkylmalonic esters. On treatment with an alkyl nitrite in alkaline solution, efficient oximation of these esters at the tertiary carbon atom is accompanied by simultaneous hydrolysis and decarboxylation of one carbethoxyl group, *i.e.*, $CHR(CO_2Et)_2 \longrightarrow HO{\cdot}N{:}CR{\cdot}CO_2H$. Now it is known that α-oximino-acids, while resistant to alkaline hydrolysis, tend to lose water and carbon dioxide in strongly acid solution with the formation of nitriles containing one less carbon atom (Bouveault and Loquin, *Bull. Soc. chim.*, 1904, 31, 1142). Yields of the nitriles thus obtained are generally poor, and, in any case, the extension of this reaction to open-chain terpenoid compounds is restricted by the sensitivity of the latter towards mineral acids, but it seemed reasonable to expect that the mineral acid could be replaced with advantage by a powerful dehydrating agent. Experiment confirmed this; the addition of acetic anhydride to a solid α-oximino-acid caused almost explosive decomposition, but the use of low-boiling petroleum as a diluent gave a high yield of nitrile.

Ethyl geranylmalonate [I; X = $CH(CO_2Et)_2$] was prepared in 50% yield † by condensing sodiomalonic ester with the geranyl chloride mixture (cf. above) and was structurally homogeneous (see below); with amyl nitrite it gave *α-oximinogeranylacetic* (*1-oximino-4* : *8-dimethyl-*n*-deca-3* : *7-dienoic*) *acid* [I; X = $C({:}NOH){\cdot}CO_2H$] in 90% yield. On crystallisation from aqueous acetone, metastable and stable forms were obtained (presumably *syn*- and *anti*-oxime isomers); the former reverted readily to the latter on subsequent recrystallisation. Smooth decomposition ensued on adding acetic anhydride to a suspension of this acid in light petroleum. The product, isolated in 70% yield, was homogeneous and analytically pure (cf. p. 927), and yielded derivatives identical with those prepared from the geranyl cyanide which had been synthesised much less satisfactorily from cuprous cyanide and geranyl chloride. The annexed reaction scheme summarises the inter-relationships of the compounds studied and records the yields of those reactions of preparative significance.

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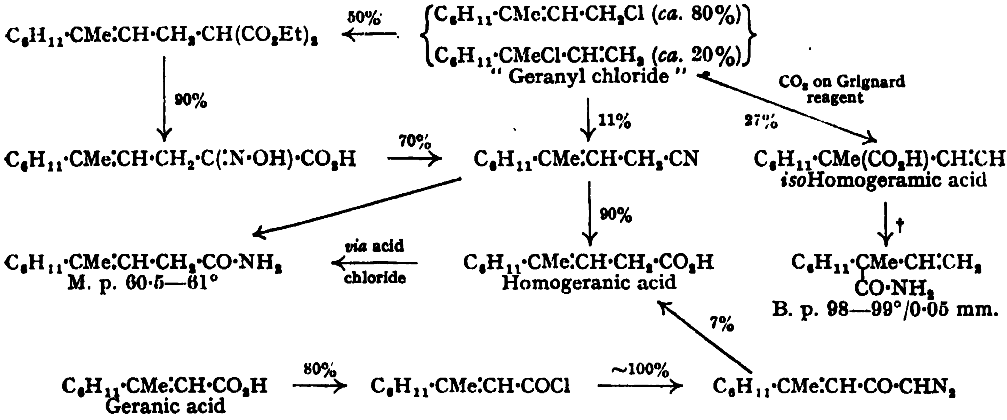
* This ratio is determined by the conditions of reaction and of subsequent isolation; it is not to be regarded as reflecting the free-energy difference between the isomers.

† The yields in this and the analogous condensations referred to later are typical for the experimental conditions employed; they may not be the highest possible.



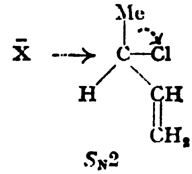
† See following paper.

The alkylated malonic ester route to cyanides provides a new method for ascending a homologous series which is especially useful for fairly reactive halides. The difficulty experienced with direct halide–cyanide exchange in these cases arises from the fact that the cyanide ion is too weak a base to initiate a bimolecular (S_N2) reaction which can compete successfully with solvolysis of the halide by the hydroxylic solvent, whose presence is demanded by solubility considerations. The heterogeneous cuprous cyanide system introduces other factors which may, or, as with geranyl chloride, may not, contribute to successful interaction. The ethyl malonate anion is not only a sufficiently powerful base to engage in effective nucleophilic attack in a hydroxylic medium, but also yields a product of unique functional character. To test the response of other allylic compounds to this synthesis, the conversion of cinnamyl chloride and of 1- and 3-methylallyl chloride into the respective cyanides has been investigated.

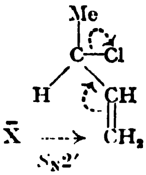
Ethyl cinnamylmalonate reacted with *n*-butyl nitrite in alkaline ethanol to give *α-oximino-cinnamylacetic* (1-*oximino*-4-*phenylpent*-3-*enoic*) *acid* (83%). This acid is dehydrated and decarboxylated extremely easily. Even repeated recrystallisation from aqueous ethanol suffices to effect complete conversion into cinnamyl cyanide, although this is effected more expeditiously in bulk by treating a light-petroleum suspension with acetic anhydride as described previously. The one preparation of this nitrile recorded (Borsche and Niemann, *Ber.*, 1936, **69**, 1993) gives a poor yield. Hydrolysis of the nitrile with alcoholic potash yielded 79% of the expected phenyl*iso*crotonic acid, $Ph{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$ (Buchner and Dessaver, *Ber.*, 1892, **25**, 1155; Fittig and Jagne, *Annalen*, 1883, **216**, 98).

Ethyl (1-*methylallyl*)*malonate* and crotylmalonate (cf. Eccott and Linstead, *J.*, 1929, 2153, and Linstead and Rydon, *J.*, 1934, 1995) were prepared from the respective chlorides in >50% yields. Since Linstead *et al.*'s samples of crotyl bromide were unquestionably heterogeneous (Winstein and Young, *J. Amer. Chem. Soc.*, 1936, **58**, 104), some doubt exists concerning the purity of these products, but, for reasons referred to below, contamination with the 1-methylallyl isomer was probably inappreciable. To free the derived esters from traces of ethyl malonate, however, very careful fractionation was necessary. The purified esters were transformed in the usual way into 1-oximino-2-methylpent-3-enoic and 1-oximinohex-3-enoic acid, crystalline solids, which were dehydrated directly in ethereal solution without isolation. The cyanides were obtained in high yield, were apparently homogeneous, and exhibited physical constants in close agreement with those reported by Lane, Fentress, and Sherwood (*loc. cit.*), but were found to evolve hydrogen cyanide on distillation and were therefore not obtained analytically pure. The cause of this slight decomposition (possibly an impurity) was not further investigated as the synthetic route was considered to be sufficiently demonstrated.

Certain further observations on the sodiomalonic ester condensations deserve mention. First, 1-methylallyl chloride reacts much more slowly than its 3-methyl isomer, in accord with the quantitative data of Young and Andrews (*J. Amer. Chem. Soc.*, 1944, **66**, 421) and of Catchpole and Hughes (*J.*, 1948, 4) on the related bimolecular substitutions with ethoxide ions. Since these authors have also established that the halides undergo unimolecular solvolysis at similar rates, it follows that under conditions where both modes of halide replacement occur the production of the primary allylic malonic ester is favoured. This is undoubtedly the principal reason why the geranyl chloride (p. 928) and crotyl bromide (p. 928) mixtures yield products containing inappreciable proportions of the secondary allylic derivative. Secondly, while the malonic ester isolated from 3-methylallyl chloride possessed *entirely* the allylic structure of the parent halide, in the 1-methylallyl series this was only *mainly* so. From the crude (1-methylallyl)malonic ester was separated a small amount of a mixed ester fraction, the analysis of which indicated that about 3% of the 3-methylallyl isomer had been formed. From such product composition data alone, it is impossible, of course, to draw conclusions about the reaction mechanism, but this finding suggests the operation of the long-forecast (Hughes, *loc. cit.*), but experimentally elusive (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 8), S_N2' reaction:



S_N2



S_N2'

During the preparation of this paper, Kepner, Winstein, and Young (*J. Amer. Chem. Soc.*, 1949, **71**, 115) reported an investigation designed expressly to detect the S_N2' mechanism if operative in the reactions just considered and in the analogous condensations with 1- and 3-ethylallyl chloride. The composition of the derived malonic esters was not examined directly; instead, these were successively hydrogenated, hydrolysed, and decarboxylated, the resulting straight-chain saturated acids fractionated, and the distillates converted in portions into the benzylamine salts, whose isomeric compositions were ascertained by melting-point comparisons. By this laborious procedure, applied apparently to a single experiment, the product obtained from 1-methylallyl chloride in boiling ethanol was found to contain 10 ± 3% of 3-methylallylmalonic ester—an estimate in reasonable agreement with our value based on partial separation and analytical identification of the rearranged ester, which also refers to one experiment and is probably somewhat low. With 1-ethylallyl chloride, rearrangement occurs to a greater extent (23 ± 3%), and this is attributed to decreased S_N2 reactivity arising from increased steric hindrance to the approach of the malonate ion at the α-carbon atom. In the tertiary allylic (linalyl) chloride (III; X = Cl), this steric situation is greatly emphasised and will be an additional factor contributing to the formation of homogeneous geranylmalonic ester [I; X = $CH(CO_2Et)_2$] from the isomeric chloride mixture (cf. above). By accessory rate measurements, Kepner *et al.* further showed (i) that the condensation is a bimolecular reaction, of the first-order with respect to both allyl chloride and malonate ion, and (ii) that it proceeds much faster than unimolecular solvolysis of the chloride. On this evidence, they naturally deduce that the production of the rearranged ester from the 1-alkylallyl chlorides definitely establishes the existence of the S_N2' mechanism.

EXPERIMENTAL.

The absence of selective infra-red absorption at the frequencies 910 and 990, 965, and 835 cm.$^{-1}$, or at small recognisable displacements therefrom, is taken as characterising the absence of CH_2:CHR, *trans*-CHR:CHR', and CRR':CHR'', respectively. The experimental basis for the analytical use of infra-red spectroscopy in this sense is presented and discussed elsewhere (Barnard *et al.*, *loc. cit.*).

The micro-analyses recorded in this and the following papers were carried out in the Analytical Department of these laboratories under the direction of Dr. W. T. Chambers.

Geranic Acid.—Oxidation of commercially pure citral by alkaline silver oxide, essentially according to Semmler's directions (*Ber.*, 1890, **23**, 3556), gave a product (65%) which after careful fractionation had b. p. 99—100°/0·1 mm., n_D^{20} 1·4876.

Geranoyl Chloride.—Distilled thionyl chloride with geranic acid in the presence of pyridine gave much tar and practically none of the desired product. However, by the use of specially purified thionyl chloride under the same conditions, good yields were readily obtained. To an ice-cooled and stirred mixture of geranic acid (50 g.), anhydrous pyridine (23·7 g.), and anhydrous ether (150 ml.) was slowly added thionyl chloride (28·7 ml.), freshly purified by successive distillation from quinoline and linseed oil. After filtration from the precipitated pyridine hydrochloride, the filtrate was refluxed for 1 hour. Removal of solvent and fractionation of the residue gave *geranoyl chloride* (81%) as a colourless liquid, b. p. 77—78°/0·3 mm., n_D^{20} 1·4963, d_D^{20} 0·9955 (Found: C, 64·6; H, 8·3; Cl, 18·7. $C_{10}H_{15}OCl$ requires C, 64·4; H, 8·1; Cl, 19·0%).

Isomeric Geranamides.—Geranoyl chloride (7 g.), added slowly to stirred 20% aqueous ammonia (15 ml.) at 0°, yielded an oil (5 g.), which was separated into geranamide-I (1·83 g.) and geranamide-II (0·36 g.) by the chromatographic procedure described by Caldwell and Jones (*loc. cit.*). The isomer-I crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 67·8—68·4° (Found: C, 71·8; H, 10·3; N, 8·3. Calc. for $C_{10}H_{17}ON$: C, 71·8; H, 10·3; N, 8·4%); the amide-II separated from the same solvent in lustrous plates, m. p. 61·6—61·9° (Found: N, 8·5%).

Diazomethyl 2 : 6-*Dimethylhepta*-1 : 5-*dienyl Ketone.*—Geranoyl chloride (45 g.) in ether (130 ml.) was added slowly, with efficient stirring, to a solution of diazomethane (from 139 g. of *N*-nitrosomethylurea) in ether (900 ml.) cooled to −10°. After being kept at 0° for 48 hours and at 20° for 1 hour, the reaction mixture was filtered, and the ether and excess of diazomethane were removed under reduced pressure at 26—28°. The residual diazo-ketone (46 g.) was an orange oil, b. p. 87—88°/0·05 mm., n_D^{20} 1·5395 (Found: C, 69·0; H, 8·6; N, 14·9. $C_{11}H_{16}ON_2$ requires C, 68·7; H, 8·4; N, 14·6%). Light-absorption measurements in ethanol showed intense bands at 2560 ($\varepsilon = 11{,}000$) and 3000 A. ($\varepsilon = 10{,}250$).

Rearrangement of Diazomethyl 2 : 6-*Dimethylhepta*-1 : 5-*dienyl Ketone.*—Attempted Wolff rearrangement of the diazoketone in (*a*) aqueous dioxan solution at 55° and 80°, (*b*) aqueous dioxan saturated with ammonia at 60° or under reflux, and (*c*) ethanol saturated with ammonia at room temperature or under reflux, in the presence of silver oxide or colloidal silver, produced only some tar; much unchanged diazo-ketone was recovered. In a wide survey of possible catalysts for the rearrangement of the diazo-ketone as a 10% solution in ethanol, positive promotion (as shown by nitrogen evolution) was found only with silver oxide and colloidal silver (slightly active) and with auric chloride (highly active).

Homogeranic Acid.—To a solution of diazomethyl 2 : 6-dimethylhepta-1 : 5-dienyl ketone (35 g.) in ethanol (400 ml.) and water (20 ml.) at 50°, a saturated solution of auric chloride (0·4 g.) in ethanol was added at such a rate that nitrogen evolution was approx. 30 c.c./min. After gas evolution had ceased, potassium hydroxide (12 g.) was added to the red, turbid solution, which was refluxed for 3 hours, filtered, and evaporated to 100 c.c. under reduced pressure. Water (400 ml.) was added, and the solution extracted with ether and then acidified with concentrated hydrochloric acid (20 ml.). *Homogeranic acid* separated as an oil which, dried (Na_2SO_4) and fractionated, had b. p. 110—110·5°/0·1 mm., n_D^{20} 1·4743 [Found: C, 72·5; H, 9·8%; $|^{=}$, 1·97 (catalytic hydrogenation). $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%; $|^{=}$, 2·0]. Yield, 2·5 g.

Homogeranamide.—Homogeranic acid (2 g.) in ether (3 ml.) was treated with pyridine (1 g.) and thionyl chloride (1·4 ml.) at 0°; after dilution further with ether and filtration, homogeranic acid chloride, b. p. 68—71°/0·1 mm., was obtained by evaporation. Interaction of this chloride with ammonia in ethanol, and isolation of the product in the usual way, gave an oil which rapidly solidified at room temperature. Recrystallisation from light petroleum (b. p. 40—60°) yielded *homogeranamide* as white platelets, m. p. 60·5—61° (Found: C, 72·8; H, 10·6; N, 7·9. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·6; N, 7·8%). Fractional elution from alumina following the procedure used for separating the isomeric geranamides indicated homogeneity of the amide. Its infra-red spectrum indicates that the olefinic unsaturation is of the type $R_2C\!:\!CHR$.

Geraniol.—"Geraniol Q" (Boake Roberts & Co.), purified through its calcium chloride addition compound and then fractionated, had b. p. 112·5—113·5°/13 mm., n_D^{20} 1·4765. Yield, approx. 60%. Its infra-red spectrum is incompatible with the presence of $CH_2\!:\!CHR$ groups, and therefore establishes its identity as the homogeneous primary allylic alcohol (I; X = OH).

Geranyl Chloride.—To a mixture of geraniol (200 g.), pyridine (110 g.), and anhydrous ether (200 ml.), thionyl chloride (170 g.) was slowly added with vigorous stirring and ice-cooling (cf. Forster and Cardwell, *loc. cit.*). After being kept for several hours at room temperature, the mixture was stirred with ice-water (3 l.), and the upper layer separated, washed with dilute sodium hydroxide solution until alkaline and then with water, and finally dried ($CaCl_2$). On fractionation through a 35-cm. Vigreux column, the product always exhibited a continuous boiling range, 50—105°/11 mm. or 25—55°/0·2 mm.; only the fraction, b. p. 85—105°/11 mm. or 45—55°/0·2 mm., n_D^{20} 1·4728—1·4790 (beginning and end of fraction), gave correct analytical figures for geranyl chloride (Found: Cl, 20·1—20·5. Calc. for $C_{10}H_{17}Cl$: Cl, 20·6%).

On dividing the chloride during fractionation into several fractions of increasing b. p., it was found by infra-red spectroscopy that the lower-boiling fractions contained considerable amounts of the isomeric tertiary chloride (linalyl chloride; III; X = Cl), the proportion decreasing with increasing b. p. until the fraction of highest b. p. was practically pure primary chloride (I; X = Cl). As is usual with allylic chlorides, the isomeric composition of these fractions changed on long storage or on heating them in a vacuum for a shorter period.

A freshly prepared sample of geranyl chloride, distilled at 0·2 mm. and of the boiling range given above, contains approx. 20% of the tertiary isomer (see footnote p. 927).

Geranyl Cyanide.—On mixing geranyl chloride (54 g.), pyridine (30 g.), and anhydrous cuprous cyanide (30 g.), heat was evolved and a pasty mass resulted; the paste liquefied on raising of the temperature to about 75°. After being maintained at this temperature for 2 hours, and at 100° for 0·5 hour, the dark syrup was poured rapidly into ether. The insoluble matter was separated, washed with ether, and the combined extracts were worked up in the usual way. The main product (30 g.) was a halogen- and nitrogen-free liquid, b. p. 45—87°/0·1 mm., and there was a much smaller amount (5 g.) of material, b. p. 87—94°/0·2 mm. Refractionation of the latter yielded a pleasant-smelling, very pale yellow oil, b. p. 90—91°/0·2 mm., n_D^{20} 1·4701, evidently slightly impure *geranyl cyanide* (Found: C, 79·7; H, 10·5; N, 7·8. $C_{11}H_{17}N$ requires C, 81·0; H, 10·5; N, 8·6%).

Hydrolysis of Geranyl Cyanide.—Geranyl cyanide (5 g.) was refluxed for 6 hours with 20% aqueous ethanol (80 ml.) containing potassium hydroxide (5 g.); no more ammonia was then evolved. The resulting acid (2·6 g.), b. p. 108—9°/0·05 mm., n_D^{20} 1·4744 (Found: C, 72·3; H, 10·0. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·9%), was identical with the homogeranic acid previously isolated, and gave, *via* its acid chloride, homogeranamide m. p. 59—59·5°, mixed m. p. 60·0—60·5°.

Geranyl cyanide (3·5 g.) was dissolved in ethanol (20 ml.) containing sodium hydroxide (1 ml.; 6N.), and 30% hydrogen peroxide (9 ml.) was added. Rapid effervescence occurred with the intermediate formation of a crystalline complex which subsequently re-dissolved. The solution was kept at 50° for 4 hours, and a crystalline product (3 g.) then isolated by ether-extraction. Several recrystallisations from light petroleum (b. p. 40—60°) yielded pure homogeranamide, m. p. 60·0—60·5°.

Ethyl Geranylmalonate.—Redistilled ethyl malonate (126 g.) was added during 30 minutes to a hot solution of sodium (17·8 g.) in anhydrous ethanol (750 ml.). Geranyl chloride (138 g.) was then added with vigorous stirring at a rate sufficient to keep the solution gently refluxing. Heating was continued until the mixture was neutral to moist litmus (2 hours), whereafter most of the ethanol was removed by distillation. The oil obtained by pouring the residue into water gave, on fractionation, much low-boiling material together with the desired product (100 g.), b. p. 126—129°/0·2 mm., n_D^{20} 1·4610 (Found: C, 68·9; H, 9·6. Calc. for $C_{17}H_{28}O_4$: C, 68·9; H, 9·5%). The infra-red spectrum indicates the absence of $CH_2{:}CHR$ groups, and thus identifies the product as a primary allylic geranyl derivative.

α-Oximinogeranylacetic Acid.—Sodium (7·8 g.) was dissolved in ethanol (200 ml.), and ethyl geranylmalonate (100 g.) added slowly at 0°; *n*-amyl nitrite (43 g.) was then added dropwise with vigorous stirring. After removal of the ethanol under reduced pressure at 30°, the red residue was mixed with crushed ice (130 g.), acidified with 25% aqueous sulphuric acid (100 ml.), and extracted with ether. The ethereal extract was washed with 10% sodium hydroxide solution (6 × 50 ml.) until colourless and the aqueous solution thus obtained heated for 15 minutes on the steam-bath, the dissolved ether being distilled off. On acidification at 0°, a yellow solid (62 g.) was precipitated which was dried in a vacuum. Crystallisation was effected most readily by dissolution in boiling acetone, addition of water to cause slight turbidity, and then storage at 0°. *α-Oximinogeranylacetic* (*1-oximino-4* : *8-dimethyl-*n*-deca-3* : *7-dienoic*) *acid* was first obtained as colourless platelets, m. p. 138—139°, but the m. p. decreased with successive crystallisations to a constant value of 102·0—102·2°, the crystalline form now being needles (Found: C, 64·0; H, 8·1; N, 6·2%; equiv., 222. $C_{12}H_{19}O_3N$ requires C, 63·9; H, 8·5; N, 6·2%; equiv., 225).

Dehydration of α-Oximinogeranylacetic Acid.—The finely powdered, crude product (87 g.) was suspended in light petroleum (b. p. 60—80°; 200 ml.), and acetic anhydride (100 ml.) added slowly with stirring. Carbon dioxide was smoothly liberated, and the heat of reaction was sufficient to induce gentle boiling. The resulting solution was stirred with water for 2 hours and the undissolved oil worked up in the usual manner and fractionated. The product (43 g.), b. p. 81—82°/0·1 mm., n_D^{20} 1·4698, appeared to be identical with the geranyl cyanide obtained previously (Found: C, 80·8; H, 10·3; N, 8·4%). Hydrolysis with alkaline hydrogen peroxide yielded a crystalline amide, m. p. 60·0—60·5° alone or mixed with the original homogeranamide.

Homogeranic Acid.—Geranyl cyanide, obtained *via* the oximino-acid derivative, was hydrolysed with alcoholic potassium hydroxide solution as described previously, and an acid isolated, in 90% yield, identical with the original homogeranic acid (p. 930), b. p. 110—110·5°/0·1 mm., n_D^{20} 1·4743 (Found: C, 72·4; H, 9·9%). The infra-red spectrum of this acid indicates that olefinic unsaturation is only of the type $R_2C{:}CHR$, thus confirming that no shift of the double bond accompanies the hydrolysis. The absence of side reactions during the latter process is further confirmed by the fact that samples of homogeranamide prepared from the acid and by mild hydrolysis of the cyanide exhibited identical light absorption in the ultra-violet region.

Ethyl Cinnamylmalonate.—Under the above experimental conditions, cinnamyl chloride (142 g.) reacted with ethyl sodiomalonate (from 164 g. of ethyl malonate) to give *ethyl cinnamylmalonate* (130 g.), b. p. 137—140°/0·1 mm., n_D^{20} 1·5139 (Found: C, 69·4; H, 7·1. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%). Its infra-red spectrum establishes the absence of isomer containing the $CH_2{:}CHR$ grouping.

α-Oximinocinnamylacetic Acid.—Treatment of ethyl cinnamylmalonate (119 g.) with *n*-amyl nitrite in the manner already described yielded *α-oximinocinnamylacetic* (*1-oximino-4-phenylpent-3-enoic*) *acid* (73 g.), which crystallised from aqueous ethanol in white needles, m. p. 132—133·5°. On further recrystallisations, the m. p. steadily decreased until ultimately complete conversion into cinnamyl cyanide was realised.

Cinnamyl Cyanide.—Dehydration of crude α-oximinocinnamylacetic acid (67 g.) with acetic anhydride gave cinnamyl cyanide, m. p. 59·1—59·3° (after recrystallisation from aqueous ethanol) (Found: C, 83·8; H, 6·0; N, 9·9. Calc. for $C_{10}H_9N$: C, 83·9; H, 6·3; N, 9·8%).

*3-Phenyl*iso*crotonic Acid.*—Hydrolysis of cinnamyl cyanide (10 g.) by refluxing it with alcoholic potassium hydroxide solution until ammonia was no longer liberated (24 hours) produced 3-phenyl*iso*crotonic acid (9 g.), m. p. 87—87·5° (after recrystallisation from aqueous ethanol) (Found: C, 74·2; H, 6·3%; equiv., 163. Calc. for $C_{10}H_{10}O_2$: C, 74·1; H, 6·2%; equiv., 162).

Crotonyl Alcohol.—Meerwein–Pondorff–Verley reduction of crotonaldehyde gave a product having b. p. 120·0—120·6°/760 mm., n_D^{20} 1·4295.

1- *and* 3-*Methylallyl Chloride.*—Crotyl alcohol (161 g.) was dissolved in anhydrous ether (200 ml.), and purified thionyl chloride (357 g.) slowly added with stirring at 0°. After refluxing for 1 hour the mixture was cooled to 0° and ice-water added. The ethereal layer was separated, washed with sodium carbonate solution until alkaline and then with water, and dried ($CaCl_2$). On careful fractionation through a Fenske-type column, separation of the isomeric chlorides was achieved without difficulty, but gave 1-methylallyl chloride (61 g.), b. p. 63·0—63·9°/759 mm., n_D^{20} 1·4159, and 3-methylallyl chloride (59·5 g.), b. p. 82·9—83·9°/759 mm., n_D^{20} 1·4357.

Ethyl α-3-Methylallylmalonate (*Pent-3-ene-1* : *1-dicarboxylate*).—Ethyl malonate (115 g.) was alkylated with 3-methylallyl chloride (59 g.) in the usual way; the reaction was complete in 4 hours. Fractionation of the product through a 30-cm. Vigreux column at 0·05 mm. gave fractions with steadily increasing *n*, but the use of an efficient packed column gave, after a small fore-run (7 g.) (mainly ethyl malonate), a homogeneous distillate (77 g.), b. p. 120·0—120·5°/15 mm., n_D^{20} 1·4362 (Found: C, 61·6; H, 8·6. Calc. for $C_{11}H_{18}O_4$: C, 61·7; H, 8·5%). Its infra-red spectrum reveals that olefinic unsaturation is solely of the type RCH:CHR.

Ethyl α-1-Methylallylmalonate (*2-Methylbut-3-ene-*1 : 1-*dicarboxylate*).—Ethyl malonate (115 g.) was converted into the sodio-derivative and alkylated with 1-methylallyl chloride (61 g.). The reaction proceeded slowly: after refluxing for 10 hours the mixture was still alkaline to moist litmus and an odour of the chloride remained. However, isolation of the product after this time, followed by efficient fractionation, gave the required *malonate* (83 g.), b. p. 113·0—113·8°/16 mm., n_D^{20} 1·4333 (Found: C, 61·6; H, 8·5. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·4%). Infra-red spectroscopic examination showed that the olefinic unsaturation was purely of the type CH_2:CHR. Also isolated was a small amount (3 g.) of a higher-boiling fraction, b. p. 115·5—121°/16·5 mm., n_D^{20} 1·4342—1·4354, which could not be purified further by fractionation; its infra-red spectrum showed it to be a mixture of 3- and 1-methylallylmalonate in the ratio of 3 : 1.

3-Methylallyl Cyanide.—Ethyl α-3-methylallylmalonate (76 g.) was dissolved in sodium ethoxide solution (from 8·2 g. of sodium and 250 ml. of ethanol) and converted into 1-oximinohex-3-enoic acid by the slow addition of *n*-butyl nitrite (41 g.). The crude crystalline product was dissolved in ether (200 ml.) and dried (Na_2SO_4), and the solution refluxed for 4 hours while acetic anhydride (70 ml.) was slowly added. The product was stirred with water for 1 hour, and the ethereal layer washed successively with sodium carbonate solution and water, dried (Na_2SO_4), and fractionated through a 20-cm. column packed with glass helices. The cyanide (19·6 g.) had b. p. 142·0—143·0°/763 mm., n_D^{20} 1·4220. During the fractionation, a slight evolution of hydrogen cyanide was detected, and this is perhaps reflected in the analytical figures (Found: C, 73·8; H, 9·0; N, 16·9. Calc. for C_5H_7N: C, 74·1; H, 8·6; N, 17·2%).

1-Methylallyl Cyanide.—By the above procedure, ethyl 1-methylallylmalonate (82 g.) was converted to 1-oximino-2-methylpen-3-enoic acid, which, without isolation, was dehydrated to 1-methylallyl cyanide. Again, evidence of hydrogen cyanide evolution was observed during the fractionation of the nitrile (20·1 g.), which had b. p. 124·0—124·1°/760 mm., n_D^{20} 1·4058 (Found: N, 16·9%).

British Rubber Producers' Research Association,
Tewin Road, Welwyn Garden City, Herts.

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188. *Some Reactions of Geranylmagnesium Chloride.*

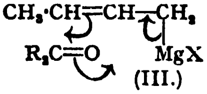
By D. Barnard and L. Bateman.

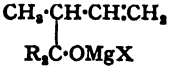
The predominantly primary allylic halide, geranyl chloride (V; X = Cl), is converted by the action of carbon dioxide or ethyl chloroformate on its Grignard derivative into the tertiary allylic acid (VI; X = CO_2H). The main by-product of these reactions is a hydrocarbon mixture derived from the combination of two geranyl fragments. This mixture, which is obtainable in better yield by direct methods, contains a higher proportion of *digeranyl* (VIII) relative to iso*digeranyl* (VII) than found in the corresponding product from related systems. The significance of this finding to the mechanism of the coupling process is discussed.

Little progress has been made in understanding the anomalous behaviour of allylic type Grignard reagents, but the recent extensive study of the butenyl derivatives by Young and his associates (reported in a series of papers, *J. Amer. Chem. Soc.*, 1936—1946) has done much to enlarge empirical knowledge. The findings and conclusions of these workers may be briefly summarised thus. In the absence of direct evidence, arguments based on certain reactivity characteristics of benzylmagnesium halides are generalised and are considered to indicate that the Grignard complex prepared from a primary allylic halide (I; X = halogen) itself possesses the primary (I) rather than the isomeric secondary allylic structure (II). No reaction is known,

$CH_3{\cdot}CH{:}CH{\cdot}CH_2X$
(I.)

$CH_3{\cdot}CHX{\cdot}CH{:}CH_2$
(II.)


(III.)


$$\begin{array}{l} CH_3{\cdot}CH{\cdot}CH{:}CH_2 \\ \quad\;\, | \\ R_2C{\cdot}OMgX \end{array}$$
(IV.)

however, whereby replacement of the magnesium halide component yields a substantially pure crotonyl derivative (I). On treatment with water or oxygen, mixtures of isomeric butenes or butenols are obtained, respectively, and coupling reactions likewise give heterogeneous products. On the other hand, reactions with carbonyl compounds lead almost exclusively to the Δ^1-olefinic derivatives (IV), the initial interaction of the two reagents being postulated as (III; R_2CO representing an aldehyde, a ketone, or carbon dioxide). This somewhat unusual behaviour may not only introduce complications in synthetic work, but also lead to erroneous conclusions concerning the structure of allylic halides deduced from such reactions (cf. Bateman, Cunneen and Koch, *Nature*, 1949, **164**, 242; following paper). Lack of diagnostic value is accentuated by the observation (Roberts and Young, *J. Amer. Chem. Soc.*, 1945, **67**, 148) that carboxylation of the Grignard compound prepared from 1-methylallyl chloride (II; X = Cl) gives the same acid (II; X = CO_2H) as is obtained by submitting the crotyl halide (I; X = Br) to the same procedure.

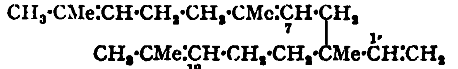
For reasons arising out of the difficulty experienced in preparing homogeranic acid (V; X = CO_2H) by standard methods (see the preceding paper), we investigated transformations of the

$$\mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2X} \quad \text{(V.)} \qquad \mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeX{\cdot}CH{:}CH_2} \quad \text{(VI.)}$$

Grignard derivatives of geranyl chloride (V and VI; X = Cl; containing *ca.* 80% of V, as usually isolated, cf. preceding paper). By infra-red spectroscopy (Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915), structural changes analogous to those observed in the butenyl series were readily followed.

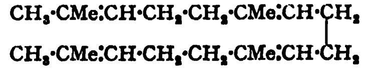
Carboxylation of the Grignard complex gave in 30% yield an acid of appreciably lower boiling point and refractive index than homogeranic acid (V; X = CO_2H). Strong infra-red absorption at 908 and 990 cm.$^{-1}$, in agreement with ozonolysis data, identifies the acid as iso*homogeranic acid* (VI; X = CO_2H). iso*Homogeranamide* (VI; X = $CO{\cdot}NH_2$), prepared *via* the *acid chloride* (VI; X = COCl), differed from its isomer (V; X = $CO{\cdot}NH_2$) (*J.*, 1950, 915) in being a non-crystallisable oil (as is the *p*-bromophenacyl ester), but the rather difficultly crystallisable *anilide*, m. p. 49—50°, may be used for characterisation. Similarly, the addition of the Grignard complex in ether to an ethereal solution of ethyl chloroformate at −10° produced an ester which was not easily purified but which on hydrolysis also yielded *iso*homogeranic acid. Insofar as the isolation and physical examination of the products permitted, no evidence of the formation of the isomeric homogeranic acid in these reactions was obtained. These results show (i) that allylic rearrangement from the primary to the tertiary structure occurs with a facility comparable to that of the corresponding primary–secondary change in similar reactions, and (ii) that chloroformic ester is a reagent of non-carbonyl function which adds at the γ-carbon atom of the allylic system.

The principal by-product from both the *iso*homogeranic acid preparations was a high-boiling hydrocarbon mixture, separable by efficient fractionation into components boiling at 171·3—171·9°/12 mm. and 178·9—179·2°/11 mm., respectively, which were present in the proportion of *ca.* 2 : 1. No crystalline derivatives of either could be prepared, but analyses, infra-red



$$\begin{array}{l}\mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}\underset{7}{C}H{\cdot}CH_2}\\ \qquad\mathrm{CH_3{\cdot}CMe{:}\underset{12}{C}H{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{\cdot}\overset{1'}{C}H{:}CH_2}\end{array}$$

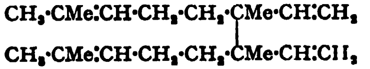
(VII.)



$$\begin{array}{l}\mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2}\\ \mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2}\end{array}$$

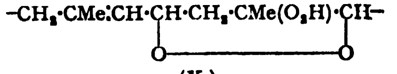
(VIII.)

spectra, and ozonolyses establish beyond doubt that the lower- and higher-boiling fractions are respectively iso*digeranyl* (VII) and *digeranyl* (VIII). Ozonolysis of the latter gave succinic acid (92%), but no formaldehyde; the former gave a crystalline acid which analysis indicates to be 2-methylbutane-1 : 2 : 4-tricarboxylic acid and which is clearly the product of oxidative scission at the 7-, 12-, and 1′-double bonds. Consistently, the latter olefin exhibited no marked infra-red absorption at 908 and 990 cm.$^{-1}$ characteristic of the presence of $CHR{:}CH_2$ groups, whereas the former did so with an intensity which virtually establishes its identity as (VII) rather than the related isomer (IX) on this evidence alone.



$$\begin{array}{l}\mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{\cdot}CH{:}CH_2}\\ \mathrm{CH_3{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{\cdot}CH{:}CH_2}\end{array}$$

(IX.)

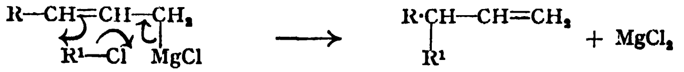


$$\begin{array}{l}\mathrm{-CH_2{\cdot}CMe{:}CH{\cdot}CH{\cdot}CH_2{\cdot}CMe(O_2H){\cdot}CH-}\\ \qquad\qquad\qquad\quad\mathrm{O{-}{-}{-}{-}{-}{-}O}\end{array}$$

(X.)

Hydrocarbon mixtures of similar composition were subsequently prepared in yields of the order of 70% by coupling geranylmagnesium chloride over silver bromide and by treating geranyl chloride directly over magnesium; (IX) was not detected. Digeranyl is the lower homologue of the naturally occuring triterpene, squalene, and has proved to be a valuable low-molecular model for studying polyisoprene reactivity. The departure from regular head-to-tail isoprene union throughout the molecule is of minor consequence in this connection. For example its oxidation characteristics closely simulate those exhibited by the long-chain polyisoprenes, gutta-percha and natural rubber hydrocarbons, both kinetically (unpublished work by Bolland and by Bateman, Bolland, and Gee) and in the unusual nature of the peroxide unit (X) in the primary product (Bolland and Hughes, this vol., p. 492; and unpublished).

The formation of the relatively high proportion of (VIII) to (VII) compared with the proportions of the related isomers derived from crotonyl and cinnamyl halides—where the forms corresponding to (VII) predominate to the extent of about 8 : 1 and 4 : 1 respectively—is an interesting feature bearing on the mechanism of the coupling process. Koch (*J.*, 1948, 1111) recently commented on the differences found in the crotonyl and the cinnamyl systems and has suggested that the factor responsible is increased resonance stabilisation of the 3-phenylallyl as compared with the 3-methylallyl grouping. The present finding with a system intermediate in such electronic character between the above groups obviously renders any simple explanation in these terms inadequate. If we assume with Young and Roberts (*J. Amer. Chem. Soc.*, 1946, 68, 1472) that the Grignard complex possesses an essentially covalent primary allylic structure,* the structural course of the reaction with a simple alkyl halide (*J.*, 1950, 941), just as with ethyl chloroformate and with chloromethyl *n*-butyl ether (Young, Roberts, and Wax, *J. Amer. Chem. Soc.*, 1945, 67, 841), requires that a " chelated " transition complex similar to that envisaged for carbonyl-compound interaction (Johnson, *J. Amer. Chem. Soc.*, 1933, 55, 3029; Young and Roberts, *loc. cit.*) promotes combination thus : †



$$\mathrm{R{-}CH{=}CH{-}CH_2MgCl + R^1{-}Cl \longrightarrow R{\cdot}CH(R^1){-}CH{=}CH_2 + MgCl_2}$$

Analogous functioning by an allyl halide can clearly account for a substantial proportion of the unsymmetrical coupled product (as VII) (cf. Johnson in Gilman, " Organic Chemistry," Wiley and Sons, New York, 2nd edn., 1943, p. 1881). However, several independent phenomena—*e.g.*, electro-chemical behaviour indicative of an ionised salt-like structure (Evans and Pearson, *J. Amer. Chem. Soc.*, 1942, 64, 2865), or the profound influence of extraneous metallic compounds, notably cobaltous chloride, on the course of Grignard reactions, probably caused by initiation of free-radical processes (Kharasch *et al.*; for a summary see *Ann. Reports*, 1944, 195; cf., however, Wilds and McCormack, *J. Org. Chem.*, 1949, 1, 45), and the small variations in reaction conditions and in the structure of the addenda which determine whether benzylmagnesium halides yield normal or abnormal (*o*-tolyl) products (Austin and Johnson, *ibid.*, 1932, 54, 647)—clearly signify that Grignard reagents possess diverse reactivity potentialities which are not distinctly separated energetically. Hence, the liberation of allylic free radicals or anions, and their participation in reactions occurring concurrently with the " chelation " process are to be expected. Any tendency exhibited in this respect by the 3-methylallyl system will be enhanced in the 3-phenylallyl and 3 : 3-dialkylallyl systems owing to the increased facility for radical or ionic dissociation afforded by the greater resonance energies of the hydrocarbon fragments thus produced. Since processes involving free allylic ions (see, *e.g.*, Catchpole, Hughes, and Ingold, *J.*, 1948, 8; Campbell and Young, *J. Amer. Chem. Soc.*, 1947, 69, 688, 3066) or radicals (Bolland and Koch, *J.*, 1945, 445; cf. *J.*, 1950, 941) invariably lead to mixtures of isomeric products, the increased heterogeneity of the hydrocarbon dimers derived from cinnamyl and geranyl halides is understandable. In comparing the last two systems among themselves, however, account must be taken of an important difference in location of the reactivity focus in the respective hydrocarbon radicals or ions. In contrast to the situation prevailing in covalent compounds—where the primary allylic isomer ($CHR{:}CH{\cdot}CH_2X$) is much the more favoured thermodynamically—experiment shows (Birch, *Faraday Soc. Discussion*, 1947, 2, 246, where other references are given), and theory readily interprets (de la Mare, Hughes, and Ingold, *J.*, 1948, 17), that the charge in a 3-arylallyl anion is sited predominantly at $C_{(\gamma)}$ ($Ar{\cdot}\overset{-}{C}H{\cdot}C{:}CH_2$), whereas in a 3-alkylallyl anion it is at $C_{(\alpha)}$ $Alk{\cdot}(CH{:}CH{\cdot}\overset{-}{C}H_2)$. Accepting that $C_{(\gamma)}{-}C_{(\gamma)}$ combination is repressed by special factors which cannot now be discussed, it is clear that this distinction—which undoubtedly exists equally in the free-radical analogues—is in accord with the experimental observations concerning the variations in $C_{(\alpha)}{-}C_{(\alpha)}$ and $C_{(\gamma)}{-}C_{(\alpha)}$ coupling in the geranyl and cinnamyl systems.

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* Two arguments additional to those advanced by Young and Roberts in support of this assumption warrant consideration. First, reactions of carbonyl compounds with the sodium derivative of allylbenzene in liquid ammonia, *i.e.*, conditions where carbanions certainly participate in the reaction, yield isomeric product mixtures (Campbell and Young, *J. Amer. Chem. Soc.*, 1944, 69, 3066), in contrast to the remarkably homogeneous secondary allylic products obtained from the corresponding Grignard reactions. Secondly, the formation of structurally analogous carbinols and acids from crotonyl- and cinnamyl-magnesium halides (Gilman and Harris, *J. Amer. Chem. Soc.*, 1931, 53, 3541) suggests strongly that these two Grignard reagents possess a common basic structure. For reasons outlined later in this paper, covalent attachment of the MgX group to the hydrocarbon component must be inferred, since in dissociated or pseudo-dissociated formulations the location of the principal reactivity centre at different points in the two hydrocarbon units should be reflected in dissimilarities of the product.

† An interpretation of the factors directing R- to the γ- rather than to the α-carbon atoms is given later (*J.*, 1950, 941).

EXPERIMENTAL.

Geranyl Chloride.—The commonly isolated isomeric mixture (cf. preceding paper) containing approx. 80% of the primary geranyl chloride (V; X = Cl) and 20% of the tertiary linalyl chloride (VI; X = Cl) has been used in the present work.

Geranylmagnesium Chloride.—The reaction leading to this Grignard reagent is difficult to start and can be markedly inefficient. The following was found to be the most satisfactory procedure. Magnesium turnings (12·5 g.) were covered with anhydrous ether (500 ml.), and 9 g. of geranyl chloride and a crystal of iodine added. A 15% solution of geranyl chloride in ether (2 ml.), vigorously reacting with a small amount of magnesium previously activated by heating with iodine, was added; on gently warming, the main reaction then started. More ether (500 ml.) was added immediately, and geranyl chloride (79 g.) dropped in at a rate sufficient to keep the mixture warm but not refluxing (2—4 hours). An atmosphere of dry nitrogen was maintained in the apparatus throughout these operations. Even in such conditions, much of the geranyl chloride participates in coupling reactions, as shown by the turbidity of the reaction mixture and by the use of less than the theoretical amount of magnesium.

iso*Homogeranic Acid.*—A rapid stream of dry carbon dioxide was passed for 2 hours into an ethereal solution of geranylmagnesium chloride, prepared as described above and maintained at −30°. The resulting mixture was cautiously treated with ice-cold 25% sulphuric acid (150 ml.), and the ethereal layer separated and extracted with 2N-sodium hydroxide. iso*Homogeranic* (3 : 7-*dimethylocta*-1 : 6-*diene*-3-*carboxylic*) *acid* (25·5 g.), thus extracted was isolated in the usual way and had b. p. 99—100°/0·05 mm., n_D^{20} 1·4668 (Found: C, 72·6; H, 10·0%; equiv., 182·4. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%; equiv., 182·0).

iso*Homogeranamide.*—Thionyl chloride (3·5 ml.) was added slowly with stirring to *iso*homogeranic acid (5·8 g.) in ether (10 ml.) and pyridine (2·6 g.). The mixture was finally refluxed for 30 minutes, then cooled, diluted with ether (30 ml.), and filtered. Fractionation of the filtrate gave the *chloride* (5 g.) as a colourless oil, b. p. 49—51°/0·1 mm., n_D^{20} 1·4754. This was added dropwise with stirring to ethanol (35 ml.) cooled to 0° and saturated with dry ammonia. After evaporation of the solvent under reduced pressure, the residue was extracted with ether. Fractionation of the extracts yielded iso*homogeranamide* as an oil (4·4 g.), b. p. 103—105°/0·05 mm., n_D^{20} 1·4920 (Found: C, 72·9; H, 10·7; N, 7·9. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·6; N, 7·8%). The infra-red spectrum of this amide exhibits strong bands at 916 and 1000 cm.$^{-1}$ indicative of the $CHR{:}CH_2$ grouping.

iso*Homogerananilide.*—*iso*Homogeranoyl chloride (2·6 g.) was added slowly to an ice-cold solution of re-distilled aniline (1·84 g.) in ether (5 ml.). After further dilution with ether (20 ml.), the filtered solution was washed with dilute hydrochloric acid, sodium hydroxide solution, and water, dried (K_2CO_3), and freed from solvent. The residual oil crystallised slowly on storage at 0°. Fractional elution from alumina using light petroleum (b. p. 40—60°), followed by sublimation at 0·05 mm., yielded the pure *anilide*, m. p. 50·5—51° (Found: C, 79·2; H, 8·7; N, 5·7. $C_{17}H_{23}ON$ requires C, 79·3; H, 9·0; N, 5·5%).

Ozonolysis of iso*Homogeranic Acid.*—The acid (1·2 g.) in glacial acetic acid (12 ml.) was treated with a slow stream of ozonised oxygen for 3 hours at room temperature. The resulting solution was dropped slowly into boiling water (100 ml.) containing suspended zinc dust (7 g.), and the volatile distillate passed into a solution of dimedon (2 g.) in aqueous ethanol. The formaldehyde–dimedon compound separated (0·30 g.), m. p. 187—188°, mixed m. p. with an authentic specimen, 188—188·5°.

Reaction of Ethyl Chloroformate with Geranylmagnesium Chloride.—The Grignard reagent prepared from geranyl chloride (106 g.) in ether (1250 ml.) was added slowly with stirring to freshly distilled ethyl chloroformate (67 g.) in ether (250 ml.) at −10°. After the addition was complete, the mixture was kept for 1 hour at room temperature and then acidified (dilute sulphuric acid), and the product in the ethereal layer recovered in the usual way. On distillation, two main fractions were collected: b. p. 100—114°/12 mm. (25 g.), and b. p. 108—118°/0·05 mm. (30 g.). The former was hydrolysed by refluxing it with potassium hydroxide (10 g.) in ethanol (200 ml.) for 4 hours. Pure *iso*homogeranic acid, b. p. 89—90°/0·01 mm., n_D^{20} 1·4669 (15 g.) was obtained. The derived chloride and amide were identical with the corresponding compounds prepared as described previously.

By-products from the Above Reactions of Geranylmagnesium Chloride.—In all the above Grignard reactions, a considerable amount of a high-boiling hydrocarbon by-product was produced, having b. p. 134—139°/0·5 mm., n_D^{20} 1·4820—1·4838. Analytical data indicated that the *substance* originated in the coupling of two molecules of the Grignard reagent (Found, lower-boiling fraction: C, 87·5; H, 12·4%; *M*, 276. Higher-boiling fraction: C, 87·6; H, 12·4%; *M*, 280. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%; *M*, 274).

Coupling Reaction of Geranylmagnesium Chloride in the Presence of Silver Bromide.—Finely ground and vacuum-dried silver bromide (155 g.) was added slowly to a vigorously stirred Grignard solution prepared from geranyl chloride (170 g.) and magnesium (24 g.) in ether (600 ml.) and maintained at 0°. Reaction was made evident by the formation of metallic silver, and completed by refluxing the mixture for 1 hour. After cooling and acidification with dilute sulphuric acid, the ethereal layer was separated and worked up in the usual way. A small portion of the product was freed from volatile material by being kept at 10^{-5} mm. in contact with a trap cooled in liquid air, and then distilled at 40°/10^{-5} mm. in a pot-type molecular still, and then had n_D^{20} 1·4828. This sample showed no change in infra-red spectrum and had almost the same *n* (1·4832) after being heated at 175° in a vacuum for 135 minutes, thus proving the absence of isomerisation [*e.g.*, from (IX) to (VIII)] under normal fractionation conditions which might mask the true composition of the coupled product. The bulk of the material was distilled from sodium (b. p. 132—137°/0·5 mm.; 102 g.), and then carefully fractionated through a Fenske-type column packed with glass helices (11 theoretical plates); later fractionations were carried out using a column packed with gauze rings (22 theoretical plates) with similar results. Separation into two homogeneous fractions was achieved with very little fore-run and residue; an intermediate mixture of the two fractions provided the major loss.

iso*Digeranyl* (50 g.) (2 : 6 : 9 : 13-*tetramethyl*-9-*vinyltetradeca*-2 : 6 : 12-*triene*) had b. p. 171·3—171·9°/12 mm., n_D^{20} 1·4821 (Found: C, 87·4; H, 12·6%; *M*, 277. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%;

M, 274). The infra-red spectrum reveals the presence of the unsaturated grouping $CH_2{:}CHR$ in addition to the grouping $CHR{:}CR_2$ (see preceding paper). *Ozonolysis.* A slow stream of ozonised oxygen was bubbled through a solution of the hydrocarbon (2 g.) in carbon tetrachloride (20 ml.) at −15° for 4 hours. Removal of the solvent left a semi-crystalline ozonide, which was dissolved in aqueous (50%) acetic acid (20 ml.), 30% hydrogen peroxide was added (10 ml.), and the solution boiled under reflux for 1·5 hours. After the solution had been made alkaline and extracted with ether, the re-acidified solution was extracted with ether to yield an oil which was dissolved in the minimum quantity of light petroleum (b. p. 60—80°) and kept at −5° for several days. Lustrous sheaves of crystals, which separated in small yield, had m. p. 126—127° after high-vacuum sublimation and recrystallisation from light petroleum (Found: C, 47·3; H, 6·1. $C_8H_{12}O_6$ requires C, 47·1; H, 5·9%).

Digeranyl (2 : 6 : 11 : 15-*tetramethylhexadeca*-2 : 6 : 10 : 14-*tetraene*) (24 g.) had b. p. 178·9—179·2°/11 m., n_D^{20} 1·4837 (Found: C, 87·3; H, 12·5%; *M*, 277; $\vDash$, 4·05 by microhydrogenation. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%; *M*, 274; $\vDash$, 4·00). The infra-red spectrum shows the olefinic unsaturation to be solely of the type $CHR{:}CR_2$ (see preceding paper). *Ozonolysis.* (i) Ozonised oxygen was passed slowly through a solution of digeranyl (0·5 g.) in glacial acetic acid (15 ml.) for 3 hours. The resulting solution was dropped into boiling water (100 ml.) containing zinc dust (7 g.), and the distillate passed into an ice-cold saturated solution of dimedon in aqueous ethanol. No formaldehyde derivative was obtained. (ii) Digeranyl (1·51 g.) in anhydrous carbon tetrachloride (30 ml.) was ozonised at −20° for 4·5 hours. After decomposition of the ozonide in boiling aqueous acetic acid containing hydrogen peroxide as described above and destruction of excess of peroxide by the addition of silver oxide, the solution was freed from soluble or colloidal silver compound with dilute hydrochloric acid, filtered, and concentrated under reduced pressure to *ca.* 2 ml. The succinic acid which separated was sublimed at 0·1 mm. and had m. p. and mixed m. p. 184—185° (Found: C, 41·0; H, 5·2%; equiv., 60. Calc. for $C_4H_6O_4$: C, 40·6; H, 5·1%; equiv., 59). Yield, 0·595 g. (91·5% theoretical).

Coupling Reaction of Geranyl Chloride over Magnesium.—Geranyl chloride (210 g.) was converted into the Grignard reagent in the usual manner, using, however, only half the theoretical quantity of magnesium. The product on isolation consisted largely of the digeranyl hydrocarbons (101 g.). Fractionation yielded pure digeranyl (27 g.) and *iso*digeranyl (52 g.).

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British Rubber Producers' Research Association,
Tewin Road, Welwyn Garden City, Herts.

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189. *The Reaction of Hexa-*1 : 5-*diene with* N-*Bromosuccinimide.*

By L. Bateman, J. I. Cunneen, Joyce M. Fabian, and H. P. Koch.

By analytical application, qualitative and approximately quantitative, of infra-red spectroscopy, and by conversion into known derivatives by reactions along well established structural routes, it has been demonstrated, contrary to the conclusions of Karrer and Schneider (*Helv. Chim. Acta*, 1948, **31**, 395), that the monobromide isolated from the reaction named in the title consists mainly of 1-bromohexa-2 : 5-diene, mixed with about 10% of the 3-bromo-$\Delta^{1:5}$-isomer.

During an investigation of certain allylic terpenoid bromides it became of interest to attempt the preparation of the bromide (I; X = Br) and to see whether dehydrobromination yielded hexa-1 : 3 : 5-triene. In view of the investigations of Winstein and Young (*J. Amer. Chem. Soc.*, 1936, **58**, 104), of Kharasch, Margolis, and Mayo (*J. Org. Chem.*, 1936, **1**, 393), and of Young, Richards, and Azorlosa (*J. Amer. Chem. Soc.*, 1939, **61**, 3070) into the isolation and interconversion of related allylic bromides, it was apparent from the outset that this bromide would generally co-exist with its allylic isomer (II; X = Br) and that its preparation substantially pure would present much difficulty. It was, therefore, surprising that Karrer and Ringli (*Helv. Chim. Acta*, 1947, **30**, 863) reported the preparation of (I; X = Br) by treatment of hexa-1 : 5-diene (diallyl) with *N*-bromosuccinimide in boiling carbon tetrachloride. Further bromination by the same method yielded a crystalline dibromide formulated as (III). A second, correcting paper (*idem, ibid.*, 1947, **30**, 1771) reported the dibromide to be the conjugated compound (IV; X = Y = Br) (Farmer, Larria, Switz, and Thorpe, *J.*, 1927, 2937), and doubt was expressed concerning the correctness of the structure assigned to the monobromide. This doubt was quickly resolved in favour of the original assignment by Karrer and Schneider (*ibid.*, 1948, **31**, 395), who condensed the monobromide with acetophenone in the presence of magnesium and ether, ozonised the resulting *tert.*-alcohol, and measured the liberation of 1·44 g.-mols. of

(I.) $CH_2{:}CH{\cdot}CH_2{\cdot}CHX{\cdot}CH{:}CH_2$ $\quad$ $CH_2{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2X$ (II.)

(III.) $CH_2{:}CH{\cdot}CHBr{\cdot}CHBr{\cdot}CH{:}CH_2$ $\quad$ $XCH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2Y$ (IV.)

formaldehyde; no acetaldehyde was detected. The last observation was significant since Karrer and Schneider had found that mild hydrolysis of the acetate obtained from the bromide by silver acetate produced an unsaturated alcohol which yielded *n*-hexanol on catalytic reduction. An ω-bromide structure therefore became a possibility and consideration was mainly given to (IV; X = H; Y = Br) rather than to (II; X = Br), presumably because of analogy with the dibromide structure. However, the ozonolysis apparently serves to eliminate this possibility, and requires that the formation of the primary alcohol be attributed to rearrangement occurring during its synthesis from the bromide.

The identification of diallyl monobromide * as (I; X = Br) is so contrary to expectation based on the behaviour of similar bromides (Young *et al.*, *loc. cit.*) as to provoke critical examination of the supporting evidence. Three unsatisfactory features are then evident. First, the absence of any mention of interconversion (I; X = Br) $\rightleftharpoons$ (II; X = Br) suggests that Karrer and Schneider overlooked the controlling influence on the composition of the product likely to be exerted by this ready isomerisation. Secondly, it seems that no isomerisation occurs during the monobromination stage and yet two double-bond displacements and the migration of the initially substituted bromine atom occur on further reaction. Thirdly, the presumed diagnostic criterion afforded by ozonolysis is almost certainly valueless since, in the case of the closely similar 1-methylallyl and 3-methylallyl bromides, Roberts and Young (*J. Amer. Chem. Soc.*, 1945, **67**, 148, 319; 1946, **68**, 1472) established that, irrespective of the isomeric nature of the original halide, reaction of the derived Grignard complex with carbonyl compounds yields almost pure secondary allylic derivatives.

The ever-present possibility of allylic isomerisation accompanying reaction militates severely against the successful application of purely chemical methods to solve this structural problem.† Accordingly, our investigations (which date from the appearance of Karrer and Ringli's first paper) have sought to make full use of infra-red and ultra-violet spectroscopy (cf. especially Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915).

The Composition of Diallyl Monobromide.—We find that analytically pure diallyl monobromide boiling over the temperature range reported by Karrer and Ringli and prepared either according to these authors' directions or by the modified procedures referred to later is neither (I; X = Br) nor (IV; X = H; Y = Br) but is *essentially* (II; X = Br). Its infra-red absorption spectrum exhibits a strong band at 965 cm.$^{-1}$, characteristic of the presence of the CHR:CHR grouping and absent in diallyl, as well as bands at 918 and 990 cm.$^{-1}$ caused by CH_2:CHR groups. The intensity of the latter band is approximately half that of the same absorption in diallyl. The ultra-violet absorption spectrum confirms the absence of diene conjugation.

With carbon dioxide the Grignard complex derived from the bromide yields the secondary allylic *hexa*-1 : 5-*diene*-3-*carboxylic acid* (I; X = CO_2H) (p-*bromophenacyl* ester, m. p. 32—33°), whose infra-red absorption differs markedly from the bromide but closely resembles that of the parent olefin between 900 and 1000 cm.$^{-1}$. This practically quantitative change from primary allylic type has been incontrovertibly demonstrated by Young and Roberts (*loc. cit.*) to be a general characteristic of carbonyl compound–butenylmagnesium halide reactions, and therefore we can confidently assert that while Karrer and Schneider's structure for the bromide is wrong their formulation of the *tert.*-alcohol prepared from acetophenone as (I; X = ‒CPhMe·OH) is right. When the bromide is converted into an ether by a hot concentrated solution of sodium ethoxide in ethyl alcohol, the product exhibits intense ultra-violet absorption at 2250 A., indicative of its conjugated nature and, in conformity, its infra-red absorption spectrum reveals the presence and absence of CH:CH and $CH:CH_2$ groups, respectively. The ether must therefore be either 1-*ethoxyhexa*-2 : 4-*diene* (IV; X = H; Y = OEt) or the 3-ethoxy-isomer. The location of the ultra-violet absorption maximum affords strong evidence favouring the former. This indication has been verified completely by catalytic reduction and identification of the product as *n*-hexyl ethyl ether by cleavage with hydriodic acid and conversion into *n*-hexyl*iso*thiuronium picrate, m. p. 156°. Since it is now well authenticated that bimolecular (S_N2) replacement reactions of allylic halides with ethoxyl ions lead wholly to attachment of the entrant group at the site of the displaced group (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 627; Catchpole and Hughes, *J.*, 1948, 4; Roberts, Young, and Winstein, *J. Amer. Chem. Soc.*, 1942, **64**, 2157; Young and

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* Throughout this paper, "diallyl monobromide" designates the isolated *substitution* product irrespective of its isomeric constitution.

† It should be noted that ozonolysis of allylic compounds possessing α-methylenic functional groups can provide particularly untrustworthy information (Young, McKinnis, Webb, and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 293).

Andrews, *ibid.*, 1944, 66, 421), combination of the ethoxyl group at a terminal carbon atom under the drastic S_N2 conditions employed provides independent and specific information concerning the location of the original bromine atom. The double-bond shift accompanying alcoholysis exemplifies the well-known lability of 1 : 4-dienes to such isomerisation under proton-transfer conditions. We have not repeated Karrer and Ringli's bromide ⟶ acetate ⟶ alcohol sequence since the tendency to S_N1 replacement (and therefore to isomeric mixtures) in the first stage (see, *e.g.*, Catchpole, Hughes, and Ingold, *J.*, 1948, 8) introduces ambiguity into any structural deductions. The procedure employed for isolation by the Swiss workers would hardly be likely to determine whether the alcohol said to be (IV; X = H; Y = OH) was free from (I; X = OH), and the mild hydrolytic conditions used in the second stage suggest that (II; X = OH) may also have been present.

No uncertainty attaches to the data and conclusions so far presented, but the normal existence of similar allylic bromides as isomeric mixtures containing *ca.* 15% of the secondary allylic form (Young *et al.*, *loc. cit.*), together with the fact that the bromination conditions and the subsequent isolation of the product both strongly facilitate interconversion (cf. following paper), indicate that the possibility of isolating a homogeneous diallyl monobromide as the reaction product is negligible. An immediate and affirmative indication of isomeric heterogeneity is afforded by the observation that analytically pure monobromide boils over a range of about five degrees (cf. Karrer and Ringli, *loc. cit.*). More significantly, the infra-red spectra of head and of tail fractions showed small but readily detectable variations corresponding to a higher concentration of the secondary allylic isomer (I; X = Br) in the lower-boiling material. In agreement with the work of Young *et al.* (*loc. cit.*), this partial isomeric separation on distillation was also reflected in substantial differences in refractive index. The difficult and tedious problem of accurate isomeric analysis, necessitating the separate physical characterisation of both components, is beyond the scope of the present work, but an approximate estimation can be deduced by comparing the absolute extinction coefficients of the infra-red absorption frequencies due to the CHR:CHR and CH_2:CHR groups in the bulked monobromide product. Such analysis (see the Experimental section) is complicated by the occurrence of *cis*- and *trans*-forms of the 1-bromo-Δ^2-isomer, but it is estimated that 5—15% of (I; X = Br) is present in a typical monobromide preparation.

Secondary Products of Reaction.—As reported by Karrer and Ringli (*loc. cit.*), a minor product of the diallyl–*N*-bromosuccinimide reaction is the crystalline, conjugated dibromide (IV; X = Y = Br), which is better prepared by further bromination of the monobromide and displays spectroscopic characteristics in full accord with its established molecular structure. We have also isolated a second dibromide—a liquid in which the elements of hydrogen bromide have added to the CH:CH centre of the monobromide. This compound has not been specially investigated, but its spectral properties together with knowledge of the orientation of hydrogen bromide addition to allyl bromide under similar conditions suggest fairly definitely that it is 4 : 6-*dibromohex*-1-*ene*. Small quantities of hydrogen bromide are often evolved during bromination with *N*-bromosuccinimide; larger quantities are to be expected only when spontaneous dehydrobromination is occurring simultaneously (see, *e.g.*, Dorée, McGhie, and Kurzer, *J.*, 1949, 570). Under the conditions of reaction, the bromide (II; X = Br) shows little tendency to liberate hydrogen bromide (*e.g.*, during further bromination), as might be expected from its structure, but the isomer (I; X = Br) may well do so very readily, and in doing so may provide the source of the polymeric tar which is formed in considerable quantity. Kharasch, Nudenberg, and Sternfield (*J. Amer. Chem. Soc.*, 1940, 62, 2032) have actually stated that a tendency to just this behaviour is exhibited by the corresponding chloride even at room temperature. Adequate quantities of (I; X = Br) are likely to be available for dehydrobromination on the scale required, for there is reason to believe (following paper) that (I; X = Br) and (II; X = Br) are formed in somewhat comparable amounts in the primary bromination process, although the former cannot survive isolation in amounts greater than its thermodynamic equilibrium proportion.

The Reactivity of Diallyl towards N-*Bromosuccinimide.*—Bromination proceeds far less readily with diallyl than with the singly unsaturated Δ^1-olefin, oct-1-ene (following paper), and the isoprenic diene, 2 : 6-dimethylocta-2 : 6-diene (unpublished). Our experience is that the use of the olefin in excess rather than in equimolecular porportion to the brominating agent (cf. Karrer and Ringli, *loc. cit.*) expedites reaction and lessens contamination of the monobromide with by-products. However, under conditions such that reaction with the last two olefins is complete within 15 minutes, reaction with diallyl is incomplete after two hours. Irradiation with ultra-violet light produces a small acceleration, but this is offset by an increase in secondary decomposition, shown by a marked darkening of the reaction mixture. If one accepts as a reasonable assumption, in the absence of positive evidence, that a rate-determining step in the bromination is the detachment of an α-methylene hydrogen atom (Bloomfield, *J.*, 1944, 114; cf. following paper), then the enhanced reactivity of 2 : 6-dimethylocta-2 : 6-diene compared with diallyl can readily be associated with the increased mesomerism of the methylallyl as compared with the allyl radical. The rate difference between oct-1-ene and diallyl is much less obvious, especially as Bolland (*Trans. Faraday Soc.*, in the press) has found that peroxide radicals abstract α-methylene hydrogen atoms from both molecules with practically the same efficiency—a result which should be general for any similar hydrogen exchange.

Added in proof. On the basis of ozonolysis results, Karrer and Perl (*Helv. Chim. Acta*, 1950, **33**, 36) have rejected our conclusions as presented in a preliminary note (*Nature*, 1949, **164**, 242), and identify the isolated monobromide as essentially $CHMe{:}CH{\cdot}CHBr{\cdot}CH{:}CH_2$ (V). The analytical data supporting this view are, however, inherently uncertain (cf. *J.*, 1950, 915), and it is opposed by the diverse and fully consistent evidence reported in this and the following paper, and the facts that it involves unusual prototropic changes [*e.g.*, the conversion of (V) into (I; $X = CO_2H$) during an ordinary Grignard reaction], and that 3-bromo-1 : 4-dienes do not normally exist because the lability of the bromine atom allows full rein to the conjugative tendency of the 1 : 4-diene unit [*e.g.*, attempted preparations of 1-phenylallyl bromide and linaloyl bromide always yield the isomeric cinnamyl and geranyl compounds, respectively, and diallyl dibromide is obtained as (IV; X = Y = Br) for the same reason].

EXPERIMENTAL.

Hexa-1 : 5-diene, prepared from allyl bromide (Cortese, *J. Amer. Chem. Soc.*, 1929, **51**, 2267), had b. p. 59·6°/758 mm. Its infra-red spectrum reflects unambiguously the absence of any but $CH_2{:}CHR$-type unsaturation (cf. Barnard *et al.*, *loc. cit.*).

Purchased and synthesised batches of *N*-bromosuccinimide varied greatly in efficacy. Recrystallisation from water was found to yield consistently active material.

*Reaction of Hexa-*1 : 5*-diene with* N*-Bromosuccinimide.*—(*a*) *Karrer and Ringli's conditions.* The olefin (50·5 g., 0·62 mole), *N*-bromosuccinimide (89 g., 0·5 mole), carbon tetrachloride (300 ml.), and benzyl peroxide (0·2 g.*) were refluxed for 8 hours. Removal of the insoluble succinimide and the solvent, and distillation of the liquid residue gave the following fractions of 1*-bromohexa-*2 : 5*-diene* admixed with a little 3-bromohexa-1 : 5-diene: (1) 1 g., b. p. 39—40°/11 mm., n_{D}^{16} 1·4963 (Found: C, 44·2; H, 5·7; Br, 50·2. C_6H_9Br requires C, 44·7; H, 5·6; Br, 49·7%); (2) 2·1 g., b. p. 40—41°/11 mm., n_{D}^{16} 1·4985; and (3) 9·5 g., b. p. 41—44°/11 mm., n_{D}^{16} 1·5005 (Found: C, 44·5; H, 5·7; Br, 50·1%).

(*b*) *Large excess of olefin.* The olefin (131 g., 1·6 moles), *N*-bromosuccinimide (100 g., 0·56 mole), carbon tetrachloride (230 ml.), and benzoyl peroxide (0·2 g.) were refluxed for 4 hours. Fractionation of the product gave (1) 2·9 g., b. p. 39—40°/10 mm., n_{D}^{16} 1·4970 (Found: C, 44·5; H, 5·7; Br, 50·0%), (2) 11 g., b. p. 40—41·5°/10 mm., n_{D}^{16} 1·4996, and (3) 12·3 g., b. p. 41·5—44°/11 mm., n_{D}^{16} 1·5009 (Found: C, 44·4; H, 5·7; Br, 49·7%).

(*c*) *Irradiation with ultra-violet light.* The olefin (70·5 g., 0·86 mole), *N*-bromosuccinimide (178 g., 1·0 mole), carbon tetrachloride (300 ml.), and benzoyl peroxide (0·2 g.) were irradiated with a Hanovia S. 500 mercury-arc lamp 15 cm. distant and refluxed for 2·5 hours. Two fractions of the distilled product were collected: (1) 4·2 g., b. p. 39—40°/10 mm., n_{D}^{14} 1·4980 (Found: C, 44·5; H, 5·7; Br, 50·2%), and (2) 13·9 g., b. p. 40—43°/10 mm., n_{D}^{14} 1·4990 (Found: C, 44·5; H, 5·7; Br, 49·9%).

Ultra-violet Spectrographic Examination of Diallyl Monobromide.—The bulked distillate from (*a*) displayed no selective absorption between 2200 and 3400 A.

Infra-red Spectrographic Examination of Diallyl Monobromide.—The bulked distillate from (*a*) exhibited strong infra-red absorption at 965, 918, and 990 $cm.^{-1}$. Comparison with diallyl (much stronger absorption at 913 and 990 $cm.^{-1}$, no absorption at 965 $cm.^{-1}$) and allyl bromide (strong absorption at 927 and 990 $cm.^{-1}$, no absorption at 965 $cm.^{-1}$) indicated that the product was essentially (II; X = Br).

For the reason given in the next paragraph, the ratio of the observed molecular extinction coefficient at 965 $cm.^{-1}$ to that exhibited by a pure reference compound does not afford an absolute measure of the concentration of $CH{:}CH$ units. However, comparison of the relative variations at 918 and 965 $cm.^{-1}$ in the several fractions yields a *relative* measure of the proportion of $CH_2{:}CHR$ and $CHR{:}CHR$ groups. The following optical densities (determined immediately after isolation of the fractions, using *ca.* 4% solutions in carbon tetrachloride and the same absorption cell throughout) reveal that an increase in b. p. and refractive index reflects an increase in the proportion of the primary allylic isomer (cf. Young, Richards, and Azorlosa, *loc. cit.*):

Bromide fraction.	*a*1.	*b*1.	*c*1.	*c*3.	*a*3.	*b*3.
n_{D}^{16}	1·4963	1·4970	1·4980	1·4990	1·5003	1·5009
$\log (I_0/I)_{918}/\log (I_0/I)_{965}$	1·90	1·64	1·51	1·08	1·11	1·01

In principle, two independent, absolute estimations of the isomeric composition of the bromide product are obtainable by the comparison of its extinction coefficients (i) at 918 or 990 $cm.^{-1}$ and (ii) at

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* On the scale described, Karrer and Ringli would have added 2·08 g. The essential features of the reaction are obviously insensitive to the use of an amount more in keeping with the catalytic rôle of the peroxide.

965 cm.$^{-1}$ with standard values determined from appropriate reference compounds. Since the former dual absorption is common to both isomers whereas the latter absorption is due solely to the presence of the $\Delta^{2:5}$-isomer, the second comparison is potentially the more sensitive. However, absorption at 965 cm.$^{-1}$ originates in the *trans*-form of the CHR′:CHR″ grouping only, and hence the occurrence of both *cis*- and *trans*-forms of the latter isomer would obviously vitiate this simple analysis. That this situation actually prevails was evident first from the much lower proportion of the $\Delta^{2:5}$-isomer thus estimated as compared with the proportion derived from method (i), and secondly from the occurrence of absorption at 680 cm.$^{-1}$ attributable to the *cis*-CHR′:CHR″ grouping (Kilpatrick and Pitzer, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 191; Sheppard and Sutherland, *Proc. Roy. Soc.*, *A*, 1949, **196**, footnote p. 203). Since a standard value of the extinction coefficient at 965 cm.$^{-1}$ of a *trans*-dialkylethylene is available (Hart and Meyer, *J. Amer. Chem. Soc.*, 1949, **71**, 1980),* comparison at this frequency serves to determine the concentrations of *trans*-1-bromohexa-2 : 5-diene. Technical difficulties, as well as the absence of a satisfactory standard, prohibit a corresponding quantitative determination of the *cis*-form. It is only possible, therefore, to estimate the chemical isomeric composition of the bromide mixture by method (i); as the data collected in the following table show, the results have limited accuracy. Since the absorption at 990 cm.$^{-1}$ appears to be insensitive to substitutional changes in the reference compounds, comparison at this frequency is considered to provide the more reliable estimate, correct to ±5%. By difference, *cis*-1-bromohexa-2 : 5-diene must be present to the extent of about 22%.

Compound.	Absorbing unit.	Frequency (cm.$^{-1}$).	Molecular extinction coefficient (per absorbing unit).	Composition of diallyl monobromide.	
				3-Bromohexa-1 : 5-diene (%).	1-Bromohexa-2 : 5-diene (% *trans*-).
Hexa-1 : 5-diene	CH_2:CHR	913	107		
		990	45		
Allyl bromide ...	CH_2:CHR	927	126		
		983	45		
trans-Hex-2-ene ...	*trans*-CHR:CHR	965	157 †	—	—
Bulked sample from preparation (*a*)	CH_2:CHR	918	113	5	—
		990	50	11	—
	trans-CHR:CHR	965	100	—	67

† From Hart and Meyer, *loc. cit.*

4 : 6-*Dibromohex*-1-*ene*.—Fractionation of the liquid remaining after fraction 3 from preparation (*a*) had distilled gave : (4) a mixture of increasing bromine content, b. p. 53—86°/14 mm., n_D^{20} 1·5121 (2·6 g.); and (5) a dibromide, b. p. 86—87°/14 mm., n_D^{20} 1·5215 (Found : C, 30·1; H, 4·2. $C_6H_{10}Br_2$ requires C, 29·8; H, 4·1%) (6·3 g.). Infra-red spectroscopic examination of the dibromide established the presence of CH_2:CHR groups and the absence of CHR:CHR groups; this material therefore results from the addition of hydrogen bromide either non-terminally to (II; X = Br) or terminally to (I; X = Br). In the latter case, addition is possible at the double bond nearer to, or further from, the initially substituted bromine atom. No attempt has been made to determine the structure of the product formally, but the following deductions appear to be virtually conclusive. No selective absorption occurs between 2200—3400 A., and the general absorption (*e.g.*, log ε = 3·0 at 2200 A.) is much less than that of the specimen of diallyl monobromide referred to above (*e.g.*, log ε = 3·7 at 2200 A.). This difference can only mean that allylic bromide absorption has been replaced by alkyl bromide absorption, *i.e.*, hydrogen bromide addition may have occurred at the nearer, but not at the further, double bond in (I; X = Br). In accordance with the orientation of peroxide-catalysed hydrogen bromide addition to allyl bromide (Kharasch and Mayo, *J. Amer. Chem. Soc.*, 1933, **55**, 2468), the resulting product will be the same as that obtainable from (II; X = Br), *viz.*, 4 : 6-*dibromohex*-1-*ene*.

1 : 6-*Dibromohexa*-2 : 4-*diene* (IV; X = Y = Br).—The residue left after isolating the diallyl monobromide from preparation (*c*) gave on further fractionation : (3) a monobromide–dibromide mixture, b. p. 49—87°/12 mm. (8 g.); (4) an isomeric dibromide mixture, b. p. 40—60°/0·03 mm. (14 g.); (5) 1 : 6-dibromohexa-2 : 4-diene, b. p. 60—65°/0·03 mm., m. p. 86° from light petroleum (b. p. 40—60°) (Found : C, 30·1; H, 3·4. Calc. for $C_6H_8Br_2$: C, 30·0; H, 3·3%). This dibromide exhibited typical conjugated-diene light absorption in the ultra-violet region ($\lambda_{max.}$ 2550 A., ε = 20,000); the infra-red spectrum showed no absorption at 915 and 990 cm.$^{-1}$, but very strong absorption at 965 cm.$^{-1}$. A better synthesis is : diallyl monobromide (2 g.), *N*-bromosuccinimide (2·1 g.), carbon tetrachloride (12 ml.), and benzoyl peroxide (0·01 g.) are refluxed for 6 hours; removal of volatile material under reduced pressure leaves a residue (1·6 g.) which solidifies on cooling and then has m. p. 86° (after crystallisation from light petroleum) (Found : C, 30·4; H, 3·6%).

Hexa-1 : 5-*diene*-3-*carboxylic Acid* (I; X = CO_2H).—Diallyl monobromide (10 g.) in dry ether (60 ml.) was added during 2·5 hours to a well-stirred mixture of magnesium turnings (5 g.) and ether (30 ml.). Reaction proceeded readily after initiation with a crystal of iodine. The solution of the Grignard derivative so obtained was poured quickly on powdered, solid carbon dioxide. After hydrolysis with ice and hydrochloric acid and isolation in the usual way through its sodium salt, *hexa*-1 : 5-*diene*-3-*carboxylic acid* was obtained (3·5 g.), b. p. 101—102°/12 mm. (Found : C, 66·9; H, 8·1%; equiv., 126·5. $C_7H_{10}O_2$ requires C, 66·7; H, 7·9%; equiv., 126). Its infra-red spectrum exhibits strong absorption at 915 and 990 cm.$^{-1}$, but no absorption at 965 cm.$^{-1}$ (contrast the parent bromide, p. 939). p-*Bromophenacyl hexa*-1 : 5-*diene*-3-*carboxylate* had m. p. 32—33° after crystallisation from aqueous ethanol (Found : C, 55·7; H, 4·9; Br, 24·6. $C_{15}H_{15}O_3Br$ requires C, 55·8; H, 4·7; Br, 24·8%).

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* We are indebted to these authors for an advance copy of their publication.

1-*Ethoxyhexa*-2 : 4-*diene* (IV; X = H, Y = OEt).—Diallyl monobromide (15 g.), sodium ethoxide (48 g.), and ethanol (240 ml.) were refluxed together for 3 hours. Most of the alcohol was then distilled off, water (450 ml.) added, and the mixture extracted with ether. The product isolated from the ethereal extract was 1-*ethoxy*-2 : 4-*diene* (43%), b. p. 48—49°/9 mm., n_D^{20} 1·4615 (Found : C, 75·9; H, 11·2. $C_8H_{14}O$ requires C, 76·1; H, 11·2%). The ultra-violet spectrum is characterised by : $\lambda_{max.}$ 2250 A., ε = 25,000 (in ethanol). The infra-red spectrum shows strong absorption at 965 cm.$^{-1}$, but no absorption at 915 and 990 cm.$^{-1}$. When the alcoholysis of the bromide was carried out under rather milder conditions (refluxing for 2 hours and addition of water without distilling off the alcohol), an incompletely conjugated ether was obtained, having b. p. 48—52°/15 mm., n_D^{20} 1·4572 (Found : C, 76·0; H, 11·2%).

Degradation of 1-*Ethoxyhexa*-2 : 4-*diene*.—The fully conjugated ether (5 g.) in ethanol (100 ml.) containing Adams's catalyst (0·5 g.) was shaken with hydrogen at 30 lb. per sq. inch.; *ca.* 2·3 l. of gas were absorbed in a few minutes, and no further absorption occurred during 4 hours. Isolation of the product in the usual way gave ethyl *n*-hexyl ether (4 g.), b. p. 143—145°/761 mm., n_D^{19} 1·4016 (Found : C, 73·4; H, 13·9. Calc. for $C_8H_{18}O$: C, 73·8; H, 13·9%). An authentic sample of ethyl *n*-hexyl ether had n_D^{19} 1·4017.

The hydrogenated ether (3 ml.) was refluxed with hydriodic acid (57%; 20 ml.) for 3 hours. After dilution of the cooled mixture with water, the product was recovered by ether-extraction and identified as *n*-hexyl iodide, b. p. 178°/753 mm. (2·1 g.), by conversion into *n*-hexyl*iso*thiuronium picrate, m. p. alone or mixed with an authentic specimen 156° (from ethanol) (Found : C, 40·2; H, 5·2; S, 8·0. Calc. for $C_{13}H_{19}O_7N_5S$: C, 40·2; H, 4·9; S, 8·2%).

THE BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
TEWIN ROAD, WELWYN GARDEN CITY, HERTS.

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190. *The Reaction of Oct-*1-*ene with* N-*Bromosuccinimide.*

By L. BATEMAN and J. I. CUNNEEN.

The bromination of oct-1-ene with *N*-bromosuccinimide yields a monobromide mixture analogous to that given by hexa-1 : 5-diene (preceding paper) : 1-bromo-oct-2-ene and 3-bromo-oct-1-ene are the major and minor constituents, respectively. The relative proportions of these isomers agree closely with the equilibrium mixtures formed (at 100°) by certain homologous bromides (Young, Richards, and Azorlosa, *J. Amer. Chem. Soc.*, 1939, **61**, 3070).

Different proportions of the corresponding methyloctenes are formed (*a*) by treating the bromide with methylmagnesium iodide, and (*b*) by treating the derived Grignard derivative with methyl iodide. The product from the latter reaction is structurally similar to the octene dimer produced in a Grignard coupling reaction; the significance of this finding is discussed.

The known ready interconversion of allylic bromides under the conditions of Ziegler bromination necessarily implies the isolation of an equilibrium mixture of the isomeric bromides. Any interpretation of the mechanism of the reaction based on the composition of the product is therefore valueless. However, this limitation is not generally appreciated, and hence the principles governing the composition of reaction products in allylic systems are reviewed.

IN the preceding paper, it was shown that the monobromination product obtained from hexa-1 : 5-diene (diallyl) by *N*-bromosuccinimide consisted of 1-bromohexa-2 : 5-diene containing *ca.* 10% of the isomeric 3-bromohexa-1 : 5-diene. Predominant substitution of the bromine atom at a terminal carbon atom and displacement of the relevant double bond were established unequivocally by infra-red spectrographic measurements, and by diagnostically significant substitution of the bromine by ethoxyl ions and identification of the resulting ether. However, the presence in diallyl of the second $CH_2\colon CH$ group which remains unaffected in the monobrominated product renders the demonstration of the double-bond displacement by infra-red spectral variations far less striking, and analysis of the isomeric bromide mixture far less straightforward, than would be the case with a singly unsaturated Δ^1-olefin. A parallel investigation of the bromination of oct-1-ene is therefore reported here.

For reasons not understood (preceding paper), oct-1-ene reacts far more readily with *N*-bromosuccinimide than does diallyl, and in boiling carbon tetrachloride containing a little benzoyl peroxide reaction is complete within 15 minutes. Analytically pure octene monobromide * boils over a range of about 8° and exhibits infra-red absorption which affords detailed information about its composition. In contrast to the parent hydrocarbon (I; X = H), strong absorption occurs at 965 cm.$^{-1}$, while absorption at 924 and 990 cm.$^{-1}$ is much weaker. The 965 cm.$^{-1}$

(I.) $CH_3\cdot[CH_2]_4\cdot CHX\cdot CH\colon CH_2$ $CH_3\cdot[CH_2]_4\cdot CH\colon CH\cdot CH_2X$ (II.)

band specifies the presence of $CHR\colon CHR'$; the later bands denote a reduction in the concentration of $CH_2\colon CHR$ groups. Quantitative comparison of the molecular extinction coefficient at 924 cm.$^{-1}$ of a typical reaction product of the boiling range given above with that found for the parent hydrocarbon showed the sample to consist of a mixture of *cis*- and *trans*-1-bromo-oct-2-ene (II; X = Br) and of 3-bromo-oct-1-ene (I; X = Br), containing 17 ± 3% of the latter. The proportions of the 1-bromo-Δ^2- and the 3-bromo-Δ^1-isomer in this mixture agree exactly (within experimental error) with the measured compositions of the homologous butenyl, pentenyl, and hexenyl bromides equilibrated at 100° (Young, Richards, and Azorlosa, *J. Amer. Chem. Soc.*, 1939, **61**, 3070) in which the 3-bromo-Δ^1-isomers are present to the extent of 14·5, 19·9, and 14·2%, respectively. The boiling-point variation is obviously indicative of partial isomeric separation on distillation; as with diallyl (preceding paper), differences in the infra-red spectra and refractive indices of small head and tail fractions demonstrated the accumulation of the 3-bromo- and 1-bromo-isomers in the lower- and higher-boiling material, respectively.

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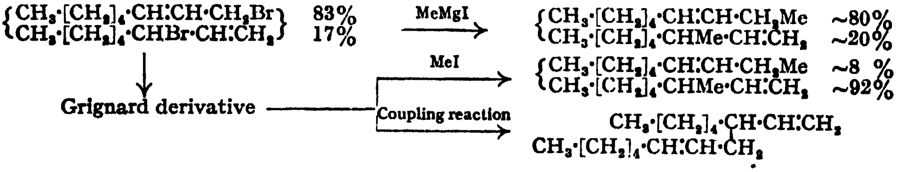
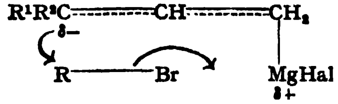
* Throughout this paper "octene monobromide" designates the isolated *substitution* product irrespective of its isomeric composition.

Carboxylation of the Grignard derivative of the octene bromide mixture yields homogeneous *oct-1-ene-3-carboxylic acid* (I; X = CO_2H) (p-*bromophenacyl* ester, m. p. 47—47·5°) which displays no infra-red absorption at 965 cm.$^{-1}$, but absorbs at 915 and 990 cm.$^{-1}$ with an intensity practically identical with that observed with oct-1-ene. This conversion of a bromide existing mainly in the primary allylic form (II) into an acid having entirely the secondary allylic structure (I) parallels exactly the behaviour of butenyl (Lane, Roberts, and Young, *J. Amer. Chem. Soc.*, 1944, **66**, 543) and geranyl (Barnard and Bateman, *J.*, 1950, 932) halides.

Reaction of the heterogeneous bromide with methylmagnesium iodide yielded a nonene mixture of (I; X = CH_3) and (II; X = CH_3) in proportion similar to those of the bromides. This finding is somewhat at variance with the product composition reported for the reaction between ethylallyl bromide (of unknown isomeric composition) and ethylmagnesium bromide (Prévost, *Compt. rend.*, 1928, **187**, 946; Prévost and Daujat, *Bull. Soc. chim.*, 1930, **47**, 588). Apart from any difference characteristic of the individual systems, the analytical procedure adopted by these authors (separate isolation and identification by oxidative degradation of the pure isomers) would appear to be quantitatively uncertain—a criticism which receives support from a similar discrepancy between the proportion of isomers produced in the Grignard coupling reaction of ethylallylmagnesium bromide as thus determined (Prévost and Richard, *Bull. Soc. chim.*, 1931, **49**, 1368) and the corresponding proportion obtained from crotylmagnesium bromide as carefully analysed by Young, Roberts, and Wax (*J. Amer. Chem. Soc.*, 1945, **67**, 841). In contrast, reaction of the Grignard derivative of the bromide with methyl iodide yielded a nonene mixture of quite different isomeric composition, the proportion of (II; X = Me) now being very small (*ca.* 8%). A similar result is derived from the structure of the hydrocarbon dimer isolated from the Grignard derivative, which proved to be essentially the unsymmetrical 6-vinyltetradec-8-ene. The reaction scheme summarises the results, which have a significant bearing on the mechanism of the coupling reaction and consequently on the nature of the Grignard derivative itself. In this example, the coupling reaction is clearly a special case of the decomposition of the Grignard compound by an alkyl halide, and illustrates the tendency of allylmagnesium halides to behave as if the MgHal unit were attached to the secondary (or tertiary) allylic, rather than to the primary allylic, carbon atom (Roberts and Young, *J. Amer. Chem. Soc.*, 1948, 1472, **68**; cf. *J.*, 1950, 932). This characteristic, which is not shared by the parent allylic halides (as the reaction now reported with methylmagnesium iodide demonstrates) could be taken as evidence that the MgHal group is actually attached to the secondary (or tertiary) carbon atom. However, Young and Roberts (*loc. cit.*) have carefully considered, and rejected, this deduction, and their arguments, although similarly inconclusive, appear very convincing. Accordingly, we interpret the mechanism of those reactions leading specifically to rearranged derivatives in terms of the intense polarity of the C–Mg bond. This polarity creates centres of high nucleophilic potential at both primary and secondary (or tertiary) carbon atoms, but since incipient ionisation of the MgHal group will be favoured by distribution of the unlike charges, reactivity at the latter position will be enhanced. Also, in reactions with alkyl halides or carbonyl compounds, the electrophilic power of the semi-cationic MgHal unit


$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2Br$ 83%
$CH_3\cdot[CH_2]_4\cdot CHBr\cdot CH{:}CH_2$ 17%
MeMgI
$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2Me$ ~80%
$CH_3\cdot[CH_2]_4\cdot CHMe\cdot CH{:}CH_2$ ~20%
MeI
$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2Me$ ~8 %
$CH_3\cdot[CH_2]_4\cdot CHMe\cdot CH{:}CH_2$ ~92%
Grignard derivative
Coupling reaction
$CH_3\cdot[CH_2]_4\cdot CH\cdot CH{:}CH_2$
$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2$

will powerfully assist the necessary polarisation of these reagents in a process sterically conducive to the mutual development of the complementary electronic displacements :



Factors enhancing the importance of alternative decompositions, and thus leading to greater complexity of reaction products in certain substituted allylic systems, are discussed elsewhere (*J*., 1950, 932).

Correlation between Reaction Mechanisms and the Composition of Products in Allylic Systems.—The contribution of the data recorded in this and the preceding paper to the understanding of the mechanism of Ziegler bromination and related reactions merits consideration, particularly as Dewar (" The Electronic Theory of Organic Chemistry," Oxford, 1949, p. 273) has recently presented a misleading argument that confirmatory evidence for a free-radical reaction mechanism would be obtained if 1-bromo-Δ^2-compounds were found to be the major products in the systems now considered.* We agree that certain features of the reaction as now conducted, *viz.*, marked catalysis by benzoyl peroxide and by ultra-violet light, afford almost compelling evidence for this type of mechanism, and the chain reaction first suggested by Bloomfield (*J*., 1944, 114) is highly plausible. Quite definitely, however, our identification of the monobromides isolated from diallyl (preceding paper) and oct-1-ene as equilibrium mixtures of the allylic isomerides offers no critical information about the course of the primary substitution process. As emphasised in a discussion of anionotropy and related reactions (Catchpole, Hughes, and Ingold, *J*., 1948, 8; de la Mare, Hughes, and Ingold, *ibid.*, p. 17), reaction products from interconvertible isomeric systems have significance in a mechanistic sense only when they are representative of *kinetic* as distinct from *thermodynamic* control, *i.e.*, the products formed in the reaction concerned are stable towards isomerisation under the conditions of reaction and subsequent isolation. Dewar dismisses the possibility of interconversion of the bromides resulting from Ziegler bromination in the sentence " Since the reaction is carried out in a non-polar solvent, the product cannot be formed by anionotropic rearrangement. . . . ." If " anionotropic rearrangement " here denotes a process in which free bromide and carbonium ions participate, this statement is literally true, but it is quite unrelated to the facts concerning the ease of isomerisation of allylic bromides (Young *et al.*, *loc. cit.*) and accordingly is irrelevant. The isomeric mobility of the liquid bromides is such that to obtain the pure isomers separately very careful and efficient fractionation at temperatures below *ca.* 20° is required. Reversion of the pure compounds to mixtures occurs readily on warming, and contaminants such as hydrogen bromide or peroxides—both of which are present in the reactions now considered—are powerful catalysts which facilitate this change even at room temperature (Kharasch, Margolis, and Mayo, *J. Org. Chem.*, 1936, 1, 393; Young *et al.*, *loc. cit.*; unpublished observations by Mr. D. B. England working in Professor Ingold's laboratory). The remoteness of kinetic control over the products isolated from the *N*-bromosuccinimide reactions also becomes obvious by reference to other systems involving bromine addition to allylic systems, *viz.*, the combination of butadiene with bromine (Farmer, Lawrence, and Thorpe, *J*., 1928, 729) and hydrogen bromide (Kharasch *et al.*, *loc. cit.*). In these cases, the futility of attempting to ascertain the initial proportions of 1 : 2- and 1 : 4-addition from experiments performed in boiling carbon tetrachloride would be universally recognised.

This aspect apart, the isolation of two isomeric diallyl or octene bromides in proportions approximating to their thermodynamic equilibrium proportions indicates that primary reaction products are not being considered. Thanks largely to work by Hughes and Ingold and by Young and their collaborators, some important principles correlating the composition of the products with reaction mechanism in allylic systems have recently become apparent. If we ignore certain special exceptions and modifications,† these, briefly, require : (i) that replacement

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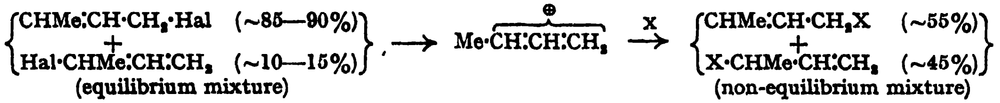
* Even more recently, Sutton and Datta (*J*., 1949, 939) have attempted to draw mechanistic conclusions from the composition of the bromine-containing products of unknown heterogeneity derived from oleic, linoleic, and linolenic esters.

† *N.B.* (*a*) The possible accompaniment of an S_N2' with an S_N2 mechanism (cf. Barnard and Bateman, *J*., 1950, 926). This is, however, difficult to realise deliberately, and circumstances conducive to its occurrence are well appreciated (Catchpole, Hughes, and Ingold, *loc. cit.*).

(*b*) Since there will be no sharp division between the conditions designated (i) and (ii), examples where " kinetically " free entities are unable to assume completely their equilibrium configurations are conceivable (Bateman, Church, Hughes, Ingold, and Taher, *J*., 1940, 979). This phenomenon is maniof an allylic substituent in a reaction where the allylic residue (ion or radical) is without free existence leads to an isomerically homogeneous product; and (ii) that in a similar replacement where the allylic residue has free existence a mixture of isomerides results such that the proportion of the less stable isomer much exceeds the equilibrium value. As the theoretical basis of this behaviour and a wide survey of its ramifications have already been presented (Catchpole, Hughes, and Ingold *loc. cit.*; de la Mare, Hughes, and Ingold, *loc. cit.*), it remains here only to cite certain examples pertinent to the investigations described in this and the preceding papers.

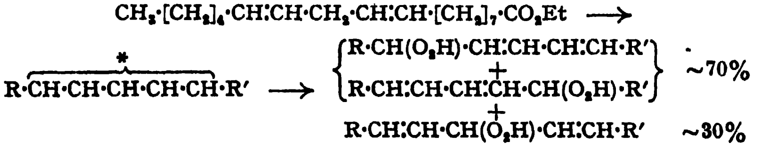
Product compositions governed by conditions (i) are clearly discernible in the interactions of allylmagnesium halides with carbonyl compounds (see, *e.g.*, *J.*, 1950, 932), where secondary (or tertiary) allylic derivatives are obtained irrespective of whether the Grignard complex is prepared from either form of pure halides or from mixtures (Young and Roberts, *J. Amer. Chem. Soc.*, 1945, 67, 148). As Young and Roberts argue, the definite structural course of these reactions implies a specific bimolecular transition state. A similar factor undoubtedly operates in the reactions between diallyl or allylbenzene and maleic anhydride or azodicarboxylic ester, where the isolated 1 : 1 adducts consist solely of hexa-1 : 4-diene or propenylbenzene (cinnamyl) derivatives (Alder, Pascher, and Schmitz, *Ber.*, 1943, 76, 27). Since the free-radical reaction mechanism postulated by Alder *et al.* cannot be seriously maintained on the evidence presented,* it is probably true, as the composition of the product indicates, that the reaction proceeds through an olefin–addendum complex, probably of the type envisaged for Diels–Alder reactions (see Koch, *J.*, 1948, 1111).

The alternative method of reaction (ii) was considered by Hughes, Ingold, and their co-workers (*loc. cit.*) for examples involving ionic allylic intermediates. Allylic free radicals should necessarily exhibit the same general behaviour, for this merely reflects commonly accepted concepts concerning mesomeric entities. Few comparative data exist, but the following are illustrative. (*a*) In methylallyl halides, the equilibrium proportion of the minor constituent, the 1-methylallyl isomer, is about 10—15% between 0° and 100° However, in reactions of the mesomeric methylallyl cation with nucleophilic addenda, combination occurs to the extent of 55% at the primary, and 45% at the secondary, allylic carbon atom :



$$\underset{\text{(equilibrium mixture)}}{\left\{\begin{array}{ll}\text{CHMe:CH·CH}_2\text{·Hal} & (\sim 85\text{—}90\%)\\ \qquad + & \\ \text{Hal·CHMe·CH:CH}_2 & (\sim 10\text{—}15\%)\end{array}\right\}} \longrightarrow \text{Me·}\overbrace{\text{CH:CH:CH}_2}^{\oplus} \xrightarrow{\text{X}} \underset{\text{(non-equilibrium mixture)}}{\left\{\begin{array}{ll}\text{CHMe:CH·CH}_2\text{X} & (\sim 55\%)\\ \qquad + & \\ \text{X·CHMe·CH:CH}_2 & (\sim 45\%)\end{array}\right\}}$$

(*b*) Autoxidation of ethyl linoleate (Bolland, *Proc. Roy. Soc.*, 1946, *A*, 186, 218) is a chain reaction in which the free radical formed by loss of a hydrogen atom from the CH_2 group of the 1 : 4-diene unit adds one molecule of oxygen, and the resulting peroxide radical then reacts with the parent ester to produce a hydroperoxide and also the original substituted pentadienyl radical. Bolland and Koch (*J.*, 1945, 445; cf. Lindberg, Chipault, and Hendrickson, *J. Amer. Oil Chemists' Soc.*, 1949 26, 109) have determined the extent to which oxygen adds centrally or terminally to the pentadienyl radical by estimating spectrographically the proportion of conjugated diene in the hydroperoxide formed; approximately 70% † of the oxidised molecules possess the rearranged structure :



$$\text{CH}_3\text{·[CH}_2]_4\text{·CH:CH·CH}_2\text{·CH:CH·[CH}_2]_7\text{·CO}_2\text{Et} \longrightarrow$$

$$\text{R·}\overbrace{\text{CH·CH·CH·CH·CH}}^{*}\text{·R}' \longrightarrow \begin{array}{ll}\left\{\begin{array}{c}\text{R·CH(O}_2\text{H)·CH:CH·CH:CH·R}'\\ +\\ \text{R·CH:CH·CH:CH·CH(O}_2\text{H)·R}'\end{array}\right\} & \sim 70\%\\ \qquad + & \\ \text{R·CH:CH·CH(O}_2\text{H)·CH:CH·R}' & \sim 30\%\end{array}$$

The small preponderance of free-radical activity at the terminal carbon atoms thus demonstrated is to be contrasted, in the same way as in (*a*), with the fact that thermal- or alkali-induced isomerisation of ***equivalently substituted*** 1 : 4- to 1 : 3-diene molecules proceeds nearly to completion.

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fested in the partial retention of activity by the products of S_N1 reactions of certain optically active halides (Bateman *et al.*, *loc. cit.*); in radical chain reactions it will clearly tend to intrude if environmental factors render the life of a radical abnormally short.

* A free radical reaction, catalysed by benzoyl peroxide occurs between natural rubber and maleinimides at a much lower temperature than the olefin–maleic anhydride reactions now referred to (Delalande, *Proc. International Congress of Pure and Applied Chem.*, London, 1947, in the press).

† In their publication, Bolland and Koch gave this figure as 70—85% owing to uncertainty as to the characteristic extinction coefficient of the pure conjugated diene. More recent data (Bergström and Holman, *Nature*, 1948, 161, 55) have largely resolved the uncertainty. We are indebted to Dr. Koch for informing us of the figure quoted.

Although data sufficiently accurate for significant comparison cannot be quoted, similar rearrangement occurs in reactions involving simple allylic radicals: a physical implication of the comparably high resonance energies of the two types of radical (allyl, 19 kcals./g.-mol.; pentadienyl, 30 kcals./g.-mol., Bolland and Orr, *Trans. Inst. Rubber Ind.*, 1945, **21**, 133) is that the similarity should be roughly quantitative, and the behaviour of allylic cations described under (*a*) affords convincing, if indirect, corroboration. Therefore, if bromination of Δ^1-olefins with *N*-bromosuccinimide proceeds by a radical chain mechanism we should expect a mixture of the 1-bromo-Δ^2- and 3-bromo-Δ^1-compounds to be formed in which the proportion of the latter is substantial, *i.e.*, probably *ca.* 40%, and certainly far more than the proportion present in the equilibrium mixture. Clearly then, the isolation of isomeric bromides from the diallyl and oct-1-ene reactions in relative amounts numerically the same as their equilibrium proportions, far from offering confirmatory evidence, is not directly related to such a mechanism.

EXPERIMENTAL.

Purchased oct-1-ene of American origin was found to contain $<1\%$ of non-terminal unsaturation. Fractionation through a Fenske-type column yielded a substantial fore-fraction, b. p. 120·1°/745 mm., free from this impurity.

Reaction of Oct-1-ene with N-*Bromosuccinimide.*—Oct-1-ene (112 g., 1 g.-mol.), *N*-bromosuccinimide (preceding paper) (63 g., 0·35 g.-mol.), carbon tetrachloride (200 ml.), and benzoyl peroxide (0·2 g.) were refluxed for 20 minutes, during which the imide reacted completely. When the product was worked up as usual, a liquid (63 g.) was obtained which on fractionation gave the following mixtures of 1-bromo-oct-2-ene (II; X = Br) and 3-bromo-oct-1-ene (I; X = Br): (1) 15·3 g., b. p. 71—73°/10 mm., n_D^{15} 1·4462 (Found: C, 50·3; H, 7·9; Br, 42·1. $C_{18}H_{15}Br$ requires C, 50·3; H, 7·9; Br, 41·9%); (2) 24·8 g., b. p. 73—79°/10 mm., n_D^{15} 1·4766 (Found: C, 50·1; H, 7·9; Br, 42·2%).

Infra-red Spectrographic Examination of Octene Monobromide.—Fractions (1) and (2) exhibited strong absorption at 965 cm.$^{-1}$ (in contrast to the parent olefin which is non-absorbing at this frequency) and weaker absorption at 924 cm.$^{-1}$ and 990 cm.$^{-1}$.

Quantitative estimation of the isomeric composition of the bulked product was carried out as described for diallyl monobromide (preceding paper). The presence of *cis*- and *trans*-1-bromo-Δ^2-isomer was again evident, but in the present example the fact that the compounds possess only one olefinic centre renders measurement of the concentration of the component $CH_2{:}CHR$ groups, *i.e.*, of 3-bromo-oct-1-ene, much more sensitive than with the mixture of substituted hexa-1 : 4- and hexa-1 : 5-dienes. The relevant data are:

Frequency, cm.$^{-1}$.	Molecular extinction coefficient: observed.	Molecular extinction coefficient: standard.	3-Bromo-oct-1-ene, %.	*trans*-1-Bromo-oct-2-ene, %.
924 *	20	117	17±3	—
965	66	150	—	44

* The strong absorption occurring maximally at 965 cm.$^{-1}$ partly overlaps the 990 cm.$^{-1}$ absorption band, and thus prevents an equivalent estimate of the $CH_2{:}CHR$ group concentration being derived.

The presence of *cis*-1-bromo-oct-2-ene (the above analysis indicates about 40%) was confirmed qualitatively by the existence of a broad absorption band at 680 cm.$^{-1}$.

Oct-1-ene-3-carboxylic Acid (I; X = CO_2H).—Octene bromide (20 g.) in dry ether (100 ml.) was added very slowly (during 2·5 hours) to magnesium turnings (8·5 g.) and ether (45 ml.). On completion of reaction (which proceeded steadily after initiation with a crystal of iodine) the solution was poured rapidly on a well-stirred excess of powdered carbon dioxide. The acidic product isolated by the usual procedure through its sodium salt proved to be the pure *oct-1-ene-3-carboxylic acid* (8 g.), b. p. 128°/11 mm. (Found: C, 69·0; H, 10·2%; equiv., 154. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%; equiv., 156). Its infra-red spectrum displayed no absorption at 965 cm.$^{-1}$ (indicating the complete absence of $CH{:}CH$ groups), but strong absorption at 915 and 990 cm.$^{-1}$. p-*Bromophenacyl oct-1-ene-3-carboxylate* had m. p. 47—47·5° after crystallisation from aqueous ethanol (Found: C, 57·9; H, 6·1; Br, 22·8. $C_{17}H_{21}O_3Br$ requires C, 57·8; H, 6·0; Br, 22·7%).

Methyloctenes.—(*a*) *From octene monobromide and methylmagnesium iodide.* Octene monobromide (10 g.) in dry ether (15 ml.) was added during 20 minutes to a slight excess of methylmagnesium iodide in ether (30 ml.). A vigorous reaction occurred after each addition of the bromide solution. When addition was complete the reaction mixture was refluxed for 15 minutes, then cooled, and treated with aqueous ammonium chloride, and the product isolated in the usual way. The following mixtures of non-3-ene (II; X = Me) and 3-methyloct-1-ene (I; X = Me) resulted: (1) 2·2 g., b. p. 130—134°/754 mm., n_D^{15} 1·4210 (Found: C, 85·5; H, 14·3. Calc. for C_9H_{18}: C, 85·7; H, 14·3%), and (2) 2·9 g., b. p. 134—136°/754 mm., n_D^{15} 1·4216 (Found: C, 85·6; H, 14·3%). The isomeric composition of these fractions was found by infra-red spectroscopic examination to correspond closely to that of the original bromide: (1) contained 15—20%, and (2) 10—15%, of the Δ^1-isomer. Since the nonene isomerides are certainly not interconvertible under the reaction conditions, this finding provides sound evidence that methyl group substitution by this process occurs at the carbon atom bearing the displaced bromine atom.

(*b*) *From octenylmagnesium bromide and methyl iodide.* To an ethereal solution of octenylmagnesium bromide (prepared as described above from 7 g. of the halide) was added methyl iodide (6 g.) in ether (10 ml.) dropwise. Vigorous interaction occurred. When all the methyl iodide solution had been added, the mixture was refluxed for 10 minutes, and the product isolated in the usual way. A non-3-ene–3-methyloct-1-ene mixture different from that produced in (*a*) was obtained, *viz.*, 2 g., b. p. 118—120°/747 mm., n_D^{17} 1·4130 (Found: C, 85·6; H, 14·5. Calc. for C_9H_{18}: C, 85·7; H, 14·3%). From the

infra-red absorption intensities at 910 and 990 cm.$^{-1}$ (strong) and at 965 cm.$^{-1}$ (weak), the concentration of 3-methyloct-1-ene was estimated to be *ca.* 92%.

Dimerised Octene.—The Grignard derivative prepared from 6 g. of octene monobromide was refluxed in ether for 10 minutes, cooled, and decomposed with ice and dilute hydrochloric acid, and the product collected in the usual way and fractionated. After a fore-run of some octene, a fraction, b. p. 135—136°/13 mm., n_D^{19} 1·4503 (Found: C, 86·5; H, 13·7. $C_{16}H_{30}$ requires C, 86·4; H, 13·6%) (3 g.), was collected. The near constancy of the boiling point offers strong evidence of structural homogeneity, and, since the relative intensities of infra-red absorption at 965, 910, and 990 cm.$^{-1}$ indicate that CH_2:CHR and CHR:CHR groups are present in similar concentration, this hydrocarbon is considered to be **9-*vinyltetradec-6-ene***, possibly contaminated with a small amount of isomer.

The work described in this and the preceding paper forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association.

British Rubber Producers' Research Association,
48 Tewin Road, Welwyn Garden City, Herts.

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191. *The Uptake of Alkali Metals by Bacteria.*

By T. C. N. Carroll, C. J. Danby, A. A. Eddy, and Sir Cyril Hinshelwood.

By means of radio-active tracers the uptake of potassium, rubidium, and sodium ions by a strain of *Bact. lactis aerogenes* growing on a single synthetic medium has been investigated.

The heaviest growth is supported by potassium, but the cells can also take up rubidium and they can accumulate potassium and rubidium in the ratio 5:2 from a medium containing roughly equal concentrations of these two ions. They are, however, unable to take up detectable amounts of sodium from a mixture of sodium and rubidium. The accumulation of rubidium in the bacteria under the conditions of the test amounted to about 60% of the total present. Previous work has shown the corresponding figure for potassium to be 97%.

That the ion which actually finds its way into the cells is really rubidium was verified by measuring the radio-active decay constant of bacteria grown in presence of active rubidium and subsequently dried.

It has previously been shown (Danby, Eddy, and Hinshelwood, *Proc. Roy. Soc.*, *B*, 1950, **136**, 544) that, as might be expected from much previous work on cells of different kinds, the presence of potassium is essential for the growth of *Bact. lactis aerogenes* in various synthetic media containing simple carbon and nitrogen sources. (References to the work of Conway and O'Malley, Leibowitz and Kupermintz, Pulver and Verzar, and others are given in the publication cited.) With the available chemical reagents an amount of potassium sufficient to support a small bacterial population (60 millions/ml.) was always present but further additions of potassium chloride increased this population linearly. Of the other alkali ions, rubidium alone seemed capable of filling the rôle of potassium in the cell, additions of rubidium chloride raising the population, though less effectively than did corresponding amounts of potassium chloride.

A detailed study of the relations between the bacterial population and the initial hydrion and potassium concentrations in glucose–ammonium sulphate media showed that hydrion antagonises the action of potassium. The facts were confirmed by measurements of the uptake by the cells of the radio-active isotope ^{42}K. In the range where the population was dependent on the potassium concentration the bacteria could take up 97% of the potassium available in the medium. This could be washed out of the cells by acid.

In the present work these observations have been confirmed and extended. In the first place, proof was desired that rubidium did in fact enter the cells and that the growth had not been due to impurities of potassium. ^{86}Rb was therefore added to the medium. From measurements of the activity of the final culture before and after centrifugation and from the activity of the separated bacteria, it was shown that radioactivity was present in the cells. The magnitude of the decay constant, moreover, confirmed that this was in fact due to rubidium. In the second place, comparisons were made of the uptake of the three ions sodium, potassium, and rubidium by use of the appropriate isotopes. The result showed that rubidium can be taken up in competition with potassium but less readily, while sodium is not taken up at all from a mixture of sodium and rubidium.

Methods.—The methods for the cultivation of the bacteria were those previously described (reference above), a standard strain of *Bact. lactis aerogenes* being maintained by serial subculture at 40·0° in a medium containing glucose, ammonium sulphate, magnesium sulphate, and an ammonium phosphate buffer. For the experiments to be described suitable additions of the appropriate alkali metals were made to the medium as required. The changes in cell population were determined by a turbidimetric technique calibrated with suspensions of known count.

The radio-active alkali metals were obtained by neutron irradiation of the carbonates at A.E.R.E., Harwell. The weighed samples of active materials were neutralised with the calculated quantity of acid and standard solutions made up. From activity measurements on these standards and the known half-lives of the radio-elements the relation between the observed rate of count of a sample at any time and the concentration of the corresponding alkali metal could be obtained.

The activity measurements were made with a liquid-type Geiger counter of about 10-ml. capacity. The electronic counting equipment followed conventional lines and was built in the laboratory. The recovery time of each Geiger tube was measured with a calibrated oscilloscope and a paralysis–time circuit in the amplifier set to a value some 10% greater, the appropriate corrections being applied to the observed rates of count.

The problem arose of determining the activity of a bacterial suspension which had been separated from an active supernatant liquid. Since it is impossible to remove all adhering fluid by centrifugation, and washing of the cells is not permissible, a method similar to the method of residues in phase-rule studies was adopted. For example, 10 ml. of a suspension were centrifuged and 9 ml. of the cell-free supernatant liquid taken for test. The remaining 1 ml. was left with the cells. From a knowledge of the activity of this concentrated suspension and of the supernatant liquid itself the activity of the cells themselves is calculable.

The similarity between the half-lives of ^{24}Na (14·8 hours) and ^{42}K (12·4 hours), and the fact that they are both γ-emitters, makes it difficult to analyse a mixture of the two either by measurement of the decay curves or by absorption measurements. But each component in a mixture of ^{86}Rb and ^{24}Na, or of ^{86}Rb and ^{42}K, can be readily estimated, since ^{86}Rb is a simple β-emitter and has a half-life of 19·5 days. Accordingly, the form of the composite decay curves was used to determine the amounts of the individual ions taken up by cells grown on the one hand in mixtures of rubidium and sodium and on the other in mixtures of rubidium and potassium.

There is, in such experiments, the possibility that one of the various alkali ions, once they reach low concentrations in the medium, might be selectively taken up by the cells. It is even more likely that one or the other might suffer displacement by hydrion if the medium were allowed to become acid. To ensure that neither of these factors came into play conditions were so chosen that the maximum bacterial population which the medium could support was limited by the glucose concentration. At the value chosen there were always appreciable amounts of alkali ion remaining outside the cells, and the pH changed little from its initial value of 7·10.

EXPERIMENTAL.

(1) *Growth with Rubidium only.*—Tubes containing medium with the appropriate amounts of added active rubidium were inoculated and at the suitable stage of growth the contents were centrifuged, samples of 10 ml. being used. 9 Ml. of the supernatant liquid were drawn off, the remaining 1 ml. being left with the total amount of cell material. The samples were tested in a liquid counter, the original culture and the separated cells after dilution in a known ratio so as to obtain a convenient counting rate (4000—10,000 counts/minute), and the supernatant liquid after being made up to a standard volume with water. From the various counts and dilution factors the activity in cells and (supernatant liquid was calculated. Two independent values for the activity of the cells are obtainable, one from (separated cells with 1 ml. of liquid) and (supernatant liquid), the other from (total culture) and (supernatant liquid). The results are given in Table I (see next section).

The bacteria from one of the samples were washed and dried in a small aluminium dish, and the rate of count was determined at intervals over a period long enough to give the decay constant. The decay was compared with that of standard ^{86}Rb samples prepared from the stock solution directly.

(2) *Growth with Rubidium and Sodium.*—A culture medium was made up to contain approximately 10 g.-ions of active Rb and 5 g.-ions of active Na per l. The general procedure was then as described for the experiments with rubidium alone. The activities of total cultures, supernatant liquids, and separated cells were all measured (*a*) as soon as possible after growth and (*b*) after 5 days, by which time only the rubidium contributes appreciably to the total activity (^{24}Na and ^{42}K fall to about 10^{-3} of the initial activity in 6 days). By extrapolating back the readings from (*b*) one can obtain the activity due to Rb at the time of (*a*) and so the activity due to the ^{24}Na at that time. Both the activities are then extrapolated to that time at which the growth of the culture is deemed to have terminated. Factors for conversion of activity to concentration were obtained by measurements on the standard solutions and referred in each case to zero time. Results are given in Table II.

(3) *Growth with Rubidium and Potassium.*—Procedure was similar to that described under (2). The calculations are somewhat more elaborate since, in contrast with the previous case, the bacteria prove to contain both metals. The contribution from each to the activity of each kind of sample has to be worked out for various times. Extrapolation to zero time in the usual way is then possible. The results are given in Table III.

RESULTS.

(1) *Rubidium.*—The measurements recorded in Table I are values corrected for the various dilution factors. The different horizontal lines refer to various cultures sampled when growth

had proceeded to a bacterial population which is expressed in the first column as a fraction of what the particular medium could have supported had time been allowed.

It is evident that the cells take up as much as 60% of the total rubidium supplied in the medium, but that after growth has ceased they give it up again. Previous experiments with potassium showed that the loss is due to the formation of acid in the medium by the continued fermentation of the glucose.

TABLE I.

Uptake of rubidium.

Medium contained: inactive potassium, $1{\cdot}1 \times 10^{-5}$ *g.-ions/l.; radio-active rubidium,* $9{\cdot}9 \times 10^{-5}$ *g.-ions/l.;* M/40-*ammonium ion (buffer constituent).*

Growth ceased at bacterial population of 240 *millions/ml.*

Bacterial population, % of max.	Activity of whole culture.	Activity of supernatant liquid.	Activity of cells + 1 ml. of liquid.	% of total Rb taken up by cells, direct.	by difference.
75	21·2	10·5	10·7	45·7	50·5
79	20·4	10·2	10·6	46·8	50·2
85	21·3	10·3	—	—	51·6
94	20·3	8·9	12·0	54·8	55·6
98	21·1	8·8	12·3	53·9	58·4
100	20·6	8·3	12·4	56·2	59·7
12 hrs. later	22·1	25·0	1·8	0	0
12 hrs. later	22·7	25·2	1·7	0	0

(All activities are given as counts/min. $\times 10^{-4}$.)

TABLE (II).

Growth in presence of rubidium and sodium.

Medium also contained: inactive potassium, $1{\cdot}1 \times 10^{-5}$ *g.-ions/ml.;* M/40-*ammonium ion (buffer constituent).*

Growth was restricted to about 100 *millions/ml. by limitation of glucose, otherwise* 200 *millions/ml. would have been reached.*

Alkali-metal concns., gm.-ions/l. $\times 10^5$. Whole culture, Rb.	Na.	Supernatant liquid, Rb.	Na.	Alkali metal in cells (expressed as an equivalent concn. in the medium). Direct measurement, Rb.	Na.	By difference, Rb.	Na.
13·0	4·9	10·5	5·5	2·1	0	2·5	−0·6
12·6	6·3	10·4	6·3	—	—	2·2	0·0
11·9	6·5	10·0	7·9	1·7	0	1·9	(−1·4)

TABLE III.

Growth in presence of rubidium and potassium.

Medium also contained: inactive potassium, $1{\cdot}1 \times 10^{-5}$ *g.-ions/l.;* M/40-*ammonium ion (buffer constituent).*

Growth was restricted to 200 *millions/ml. by limitation of glucose, otherwise* 400 *millions/ml. would have been reached.*

Alkali-metal concns. g.-ions/l. $\times 10^5$. Whole culture, Rb.	K.	Supernatant liquid, Rb.	K.	Alkali metal in cells (expressed as equivalent concn. in medium). Direct measurement, K.	K.	By difference, Rb.	K.
9·9	10·9	6·1	2·9	2·7	5·6	3·8	8·0
8·9	13·8	5·1	2·9	—	—	3·8	10·9

The decay constant corresponding to a half-life of 19·9 days makes the identification of the alkali metal in the cells with rubidium quite certain.

(2) *Rubidium and Sodium.*—Here growth was limited by exhaustion of the glucose, the concentration of this being kept low to prevent fermentation at the end of growth. Consequently the total uptake of alkali is proportionately less than in (1). No sodium could be found in the cells in the direct test. The amount found by the difference method was either zero or, as a result of manipulative losses, negative (Table II).

(3) *Rubidium and Potassium.*—Here again growth was deliberately controlled by limitation of glucose supply so that rubidium and potassium should complete on approximately equal terms throughout. The total uptake is therefore far less than it could be. The amount of

rubidium consumed is approximately 40% of the potassium. The actual form of the radioactive-decay curves confirmed the presence of the two metals with their respective half-lives (Table III).

One of the authors (A. A. E.) is in receipt of a maintenance grant from the Institute of Brewing.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, December 22nd,* 1949.]

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192. *Germanium (Germanyl) Ferrocyanide.*

By M. PEISACH, W. PUGH, and F. SEBBA.

Ionised ferrocyanides react with acid solutions of germanium dioxide to form an insoluble white precipitate. The reaction can be used as a qualitative test for germanium and, under proper conditions, leads to a product of definite composition, namely *germanyl ferrocyanide*, $[Ge(OH)_2]_2Fe(CN)_6$ or $(GeO)_2Fe(CN)_6,2H_2O$.

INSOLUBLE ferrocyanides of quadrivalent titanium, zirconium, thorium, and tin are well known (Gmelin, " Handbuch der Anorganischen Chemie," 8th Edn., System No. 59, Part B, 1930, p. 604), but no corresponding compound of germanium has been described hitherto. Many years ago, one of us (F. S.) observed that a white precipitate appeared when an acid solution of germanium chloride was treated with potassium ferrocyanide. The nature of this precipitate and the conditions necessary for the preparation of *germanyl ferrocyanide* are now described.

The formation of a white precipitate, or even a colloidal opalescence, on treatment with ferrocyanide may well serve as a useful qualitative test for germanium. This element is usually associated in minerals with arsenic and is separated from other metals by distillation of the volatile chloride from hydrochloric acid solutions. However, even with the utmost precautions to keep arsenic in the quinquevalent state the distillate contains some arsenic which then inteferes with the simple test for germanium by precipitation as the white sulphide. Neither tervalent nor quinquevalent arsenic gives a precipitate with ferrocyanides (Gmelin, *op. cit.*, p. 607). Hence, if the distillate is treated with potassium ferrocyanide solution the appearance of a precipitate is evidence of the presence of germanium. One part of germanium in 10,000 parts of solution gives an opalescence; larger amounts give a white gelatinous precipitate.

The nature and appearance of this precipitate vary with the conditions. In slightly acid solution there may be a time lag of an hour or more before precipitation, but it is shortened by increasing the acidity of the solution and by raising the temperature; the optimum conditions appear to be an acidity at least equivalent to 4N-hydrochloric acid and a temperature of 50—60°. The appearance of opalescence or a precipitate, depending on the concentration of germanium, is then a matter of seconds. Sulphuric, acetic, and chloroacetic acid are much less effective in coagulating the initial sol; and if the temperature exceeds 70° the inital white precipitate becomes blue rather quickly.

This colour change is undoubtedly due to the formation of Prussian-blue by decomposition of the excess of ferrocyanide in the strongly acid solution (Gmelin, *op. cit.*, p. 584). It takes place slowly in the cold, even in the dark and in the absence of air, but rapidly if a large excess of ferrocyanide is employed. Consequently, in the early part of the work it was impossible to get a product of uniform composition. Later, it was found that if the ratio of ferrocyanide to germanium does not exceed one g.-ion per g.-atom the precipitate darkens only slowly during several days. This is fortunate because the gelatinous precipitate cannot be filtered off and, as it is highly retentive of adsorbed electrolytes, its washing by decantation and centrifugation occupies several days. Under the most favourable conditions encountered the final product had acquired a pale mauve tinge. This product was found to contain two atomic proportions of germanium for each ferrocyanide radical and its analysis corresponds with the empirical formula $(GeO)_2Fe(CN)_6,2H_2O$ or $[Ge(OH)_2]_2Fe(CN)_6$. *X*-Ray structure analysis is the only means of establishing unequivocally which is the actual structure. No compound even approximating in composition to $GeFe(CN)_6$ has been detected in this work, and this is in accord with the general chemistry of germanium, for there is no recorded compound of this element in which the occurrence of a simple quadrivalent germanium ion has been estalished.

A similar zirconyl ferrocyanide, $(ZrO)_2Fe(CN)_6$, has been described by Weibull (*Lunds Univ. Arsskr.*, 1881—82, II, 18, No. 5, 40), though Venable and Moehlmann (*J. Amer. Chem. Soc.*, 1922, **44**, 1705) obtained products with ferrocyanide-zirconyl ratios as high as 3 : 4. Our experience with the germanium ferrocyanide leads us to suspect, however, that the American authors' products were highly contaminated with Prussian-blue.

EXPERIMENTAL.

Germanyl Ferrocyanide.—Pure germanium dioxide (4 g.) was dissolved in hot 5N-sodium hydroxide (100 ml.). The solution was diluted to 400 ml., filtered from a trace of undissolved oxide, neutralised with hydrochloric acid, and treated with concentrated hydrochloric acid to bring the acidity to 5N. The temperature was adjusted to 60°. Precipitation was made with 0·2M-potassium ferrocyanide (200 ml.).

The only practical way of washing the pure, white, bulky, and gelatinous precipitate was by settling and decantation. Because each settling period was of the order of a day the whole process of washing was extremely tedious and led to continuous darkening of the product. After the fourth wash the precipitate was dried *in vacuo* for several days, becoming then more granular. Further washing with water was then possible in a much shorter time and without appreciable decomposition. Finally, the moist precipitate was centrifuged 10 times with small amounts of ether to ensure complete removal of adsorbed hydrochloric acid. Alcohol could not be used for this purpose, for it tended to peptise the material. The product was then dried *in vacuo.*

It was a pale mauve powder which was quite stable in air and showed no tendency to become blue after many weeks' exposure to the laboratory atmosphere. Some samples that had been less thoroughly washed did become blue on storage. A thin film of Prussian-blue could often be seen over the surface of the precipitate in the centrifuge tube.

Analysis.—Germanium was determined as Mg_2GeO_4 by a modification of Muller's method (*J. Amer. Chem. Soc.*, 1922, **44**, 2493). Modification was necessary because *germanyl ferrocyanide* is insoluble in water and in acids. It does however dissolve in caustic alkalis and in aqueous ammonia. An ammoniacal solution of the sample was therefore treated with ammonium sulphate–magnesium sulphate solution, the proportions of the reagents being carefully controlled in accordance with Muller's directions. The precipitate of magnesium ammonium germanate, after being washed, was ignited to Mg_2GeO_4. The ferrocyanide in the filtrate from the germanium determination was determined, after acidification with sulphuric acid, by titration with standard permanganate by the method of de Haen (*Annalen*, 1854, **90**, 160) or with standard ceric sulphate using ferroin as internal indicator (Vogel, " Quantitative Inorganic Analysis," Longmans, 1947, p. 383). In a few cases too, the total iron was determined volumetrically after decomposition of a fresh sample with concentrated sulphuric acid (Kjeldahl). Excellent agreement was obtained by all methods.

In all, over 30 analyses were made of samples of 4 different preparations {Found: Ge, 34·2; $Fe(CN)_6$, 49·6; Fe, 13·0. $[Ge(OH)_2]_2Fe(CN)_6$ requires Ge, 34·2; $Fe(CN)_6$, 49·84; Fe, 13·1%}.

Confirmation that the compound contains either co-ordinated water or hydroxyl groups was obtained by pyrolysis. A weighed sample, mixed with copper oxide to decompose volatile cyanogen compounds, was heated in a combustion train in pure dry air and the water liberated was absorbed in " Anhydrone." The water absorbed amounted to 8·6% (Calc. for $2H_2O$, 8·5%).

Properties.—Pure germanyl ferrocyanide is a white solid which, like all other ferrocyanides, is slowly decomposed by strong acids with formation of Prussian-blue. It is insoluble in water and in moderately strong acids, but dissolves readily in alkalis, with decomposition, forming soluble germanates and alkali ferrocyanides. Heat decomposes it; at 130° it loses about one-third of its weight, and the vapours smell strongly of cyanogen compounds; at a red heat in air it loses half its weight and the vapours carry germanium as well, probably the result of reduction by carbon to the volatile germanous oxide. When desiccated *in vacuo* over sulphuric acid it becomes extremely hygroscopic; it will then absorb up to one-third of its own weight of water.

UNIVERSITY OF CAPE TOWN.

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193. *The Intramolecular Nature of the Benzidine Rearrangement.*

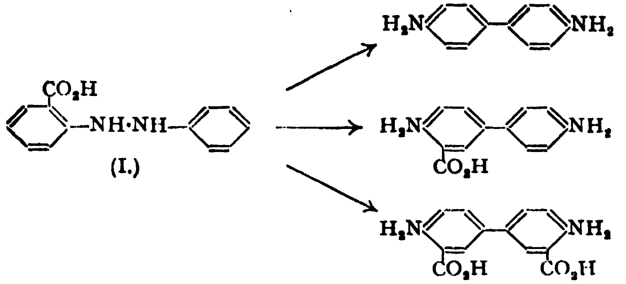
By G. J. BLOINK and K. H. PAUSACKER.

By a study of the rearrangement of unsymmetrical hydrazobenzenes, confirmation of the intramolecular nature of the benzidine rearrangement has been obtained.

ALTHOUGH there have been many formulations of the mechanism of the benzidine rearrangement (cf. Dewar, " Electronic Theory of Organic Reactions," Oxford, 1949, pp. 235 *et seq.*), there had hitherto only been one investigation (Ingold and Kidd, *J.*, 1933, 984) which determined whether the reaction was inter- or intra-molecular.

Ingold and Kidd rearranged a mixture of 2 : 2′-dimethoxy- and 2 : 2′-diethoxy-hydrazobenzene, and thermal analysis indicated that the only products were 3 : 3′-dimethoxy- and 3 : 3′-diethoxy-benzidine. Apparently no 3-methoxy-3′-ethoxybenzidine was formed in this mixed rearrangement and it was concluded that the reaction was intramolecular. As the above work depends for its conclusions on mixed melting points, it was decided to perform some experiments whereby a chemical separation of possible products could be attempted.

Accordingly, the various carboxy-substituted hydrazobenzenes were rearranged, and the products examined. If one considers the rearrangement of *2-carboxyhydrazobenzene* (I), the possible products are benzidine (II), *3-carboxybenzidine* (III), and 3 : 3′-dicarboxybenzidine (IV).


(I.) (II.) (III.) (IV.)

If the reaction is intermolecular, the principal products should be (II) and (IV) as a large difference in reactivity would be expected between the two fragments formed by an N–N fission, whereas (III) only would be formed by an intramolecular reaction. Thus the presence of (II), provided that decarboxylation does not occur, should indicate an intermolecular reaction.

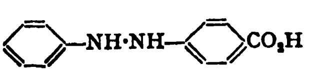
Now (II) can readily be chemically separated from (III) and (IV) owing to its non-solubility in sodium hydroxide, and thus its presence can be readily demonstrated. Furthermore, the alkali-soluble fraction will be either pure (III) or a mixture of (III) and (IV), and these two possibilities can be differentiated by both a nitrogen estimation and a determination of the acid equivalent.

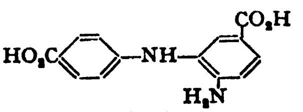
The 2-, 3-, and *4-carboxyhydrazobenzenes* were prepared by first condensing the appropriate primary amino-acid with nitrosobenzene to form the corresponding *carboxyazobenzene*. It may be noted that when either anthranilic acid or ethyl anthranilate was used, very poor yields of the azo-compound were obtained owing, apparently, to the sterically interfering *ortho*-group. These azo-compounds were then reduced to their hydrazo-analogues by means of zinc dust and sodium hydroxide, but the latter compounds were not isolated but were immediately rearranged by warming with added excess of dilute hydrochloric acid. After removal of any azo-compound by filtration, the reaction mixture was made alkaline and extracted with ether in order to isolate any benzidine formed. The alkaline solution was then weakly acidified and the amino-acids were precipitated by addition of glacial acetic acid.

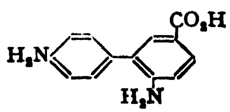
It was found that a small yield of benzidine was obtained from the rearrangement of 2-carboxyhydrazobenzene (I), indicating the possibility of an intermolecular action. However, the amino-acid gave analyses (both for nitrogen and for acid equivalent) for the mono-acid (III) and not the di-acid (IV), indicating that the benzidine had been formed by a partial decarboxylation of (III) during the course.of the reaction. As the results are not conclusive it was desirable to obtain further information from the behaviour of the other isomers.

When 3-carboxyhydrazobenzene was rearranged under the same conditions, no benzidine could be isolated from the reaction mixture and the amino-acid gave analyses corresponding to pure *2-carboxybenzidine*. This clearly indicates that an intramolecular reaction is involved and the benzidine formed during the rearrangement of (I) has only resulted by decarboxylation occurring during the reaction.

It is also of interest that when 4-carboxy- and 4-carbethoxy-hydrazobenzene (as V) were rearranged, large yields of benzidine were obtained. If one assumes an intermolecular rearrangement, then by application of the rules enunciated by Dewar (*op. cit.*, p. 234), the main products should be benzidine (II) and 4′ : 5-dicarboxysemidine (VI) along with some 5-carboxydiphenyline (VII). The amount of benzidine formed from the acid corresponded to a 74% yield if intermolecular reaction were assumed. However, the amino-acid fraction was found to be pure (VII) (nitrogen analysis and acid equivalent) and no indication of the presence of the dicarboxylic amino-acid (VI) was obtained. Thus the benzidine has once again merely resulted from a decarboxylation and not from an intermolecular reaction. This is substantiated by the fact that a gas was evolved during the rearrangement.


(V.)


(VI.)


(VII.)

In order to obtain further evidence, it was intended to investigate compounds containing a hydroxyl group in place of the carboxyl group; so once again there would be an alkali-solubilising group present which would allow the separation of any benzidine that may be formed.

However, many difficulties were encountered in this work. Owing to their ease of preparation benzeneazo-β-naphthol and 4-hydroxyazobenzene were used as starting materials. When the reduction of these compounds was attempted by the method used above, fission of the $-N{=}N-$ bond took place and appreciable amounts of aniline were isolated in each case. Catalytic reduction in the presence of Adams's catalyst (cf. Strel'tsova and Zelinskii, *Bull. Acad. Sci. U.R.S.S.*, 1941, 401) gave the same results, two moles of hydrogen being absorbed; when the reduction was stopped when only one mole of hydrogen had been adsorbed, unchanged azo-compound and aniline were isolated. However, when zinc and ammonium chloride in benzene–aqueous alcohol were used (cf. Krolik and Lukaschevich, *Chem. Abs.*, 1949, **43**, 5774) reduction appeared to take place, since the solution became colourless. Dilute hydrochloric acid was then added in order to rearrange any substituted hydrazobenzene formed and, after evaporation of the benzene and alcohol, the reaction mixture was made alkaline and extracted with ether to remove any bases formed. Evaporation of this extract yielded an almost negligible amount of substance, in both cases, which did not give any tests for benzidine (insolubility of sulphate and immediate formation of dibenzylidene derivative in alcoholic solution) or aniline (diazotisation test). This result indicates that fission of the $-N{=}N-$ linkage had not occurred during this method of reduction, since aniline was not formed. In addition, the rearrangement had not produced benzidine, thus confirming the findings obtained with the carboxy-compounds. When the aqueous solution was made slightly acidic, and excess of sodium hydrogen carbonate added, the rearrangement product was precipitated. Owing to its rapid oxidation, it could not be obtained pure even though the whole reaction had been performed in an atmosphere of nitrogen.

In order to prevent oxidation of the rearrangement product (an amino-phenol) it was decided to use the benzhydryl ethers of benzeneazo-β-naphthol and 4-hydroxyazobenzene and to remove the protecting benzhydryl group by hydrogenolysis after rearrangement. The latter benzhydryl ether was readily obtained by treatment with diphenyldiazomethane in dry benzene, but the benzeneazo-β-naphthol was recovered unchanged when similarly treated. It was found that although the above ether was readily reduced, the solution rapidly darkened during rearrangement and, as the product appeared to resist hydrogenolysis, this method of approach was abandoned.

Our work thus confirms Ingold and Kidd's postulation that this reaction is intramolecular. Since this work was completed, Wheland and Schwartz (*J. Chem. Physics*, 1949, **17**, 425) have obtained confirmatory evidence by a study of the rearrangement of an unsymmetrical hydrazobenzene by using ^{14}C as a radioactive tracer.

EXPERIMENTAL.

(M. p.s are uncorrected. Analyses are by Messrs. N. Lottkowitz and N. Gamble.)

Carboxy-substituted Compounds.—Preparation of azo-compounds. Freshly prepared nitrosobenzene (Vogel, "A Text Book of Practical Organic Chemistry," Longmans, 1948, p. 603) was condensed with the appropriate amino-compound in ethyl alcohol and glacial acetic acid under the conditions described by Wieland (*Ber.*, 1915, **48**, 1098). The reaction mixture was concentrated to obtain an additional amount of azo-compound. With 2-carboxyazobenzene it was necessary to evaporate the reaction mixture to dryness and dissolve the residue in benzene. Unchanged anthranilic acid was removed by extraction with dilute hydrochloric acid, and crude 2-carboxyazobenzene with aqueous sodium hydrogen carbonate. The latter product was precipitated by acidification of the carbonate solution and, after being extracted with ether, was crystallised from light petroleum (b. p. 60—90°).

The following table summarises the pertinent data for these compounds:

Substituted azobenzene.	Yield, %.	M. p.	Crystal form.	Solvent.	N (found), %.
2-*Carboxy-*	11	91—92°	Yellow needles	Light petroleum (b. p. 60—90°)	12·3
3- ,, ...	21	169	Light orange prisms	Alcohol	12·7
4- ,, ...	56	247	Orange plates	Alcohol	12·2

$C_{13}H_{10}O_2N_2$ requires N, 12·4%.

4-Carbethoxyazobenzene (m. p. 87°; 27% yield) was also prepared by the above method. Wieland (*loc. cit.*) gives m. p. 86—87°.

Reduction of the substituted azobenzene and rearrangement of the hydrazobenzene formed. The azobenzene (5 g.), dissolved in 2·5N-sodium hydroxide solution (50 ml.), was heated (0·75 hour) in a boiling water-bath with zinc dust (7 g.). The colourless solution was decanted and 2·5N-hydrochloric acid (150 ml.) added, whereupon a precipitate was obtained. Heating was continued (1 hour) and any solid present (identified as azo-compound formed by atmospheric oxidation) was filtered off. The solution was then basified and extracted with ether. The benzidine thus obtained was identified as its dibenzylidene derivative (m. p. and mixed m. p. 233°). The alkaline solution was acidified with acetic acid, the amino-acid fraction then being precipitated. It was purified by dissolution in hot dilute hydrochloric acid (charcoal) and precipitated as colourless micro-crystals by addition of excess of sodium acetate. If any zinc salts were present, they were removed by heating the solid with sodium hydrogen carbonate solution and the amino-acid was precipitated by addition of acetic acid. When 4-carbethoxyazobenzene was used, the reduction was carried out in alcoholic sodium hydroxide. Simultaneous hydrolysis took place, for the amino-acid obtained by rearrangement was identical with the product formed from 4-carboxyazobenzene.

The results obtained are summarised below :

Initial compound.	Azo-compound recovered, g.	Wt. of benzidine, g.	Wt. of amino-acid, g.	M. p. of amino-acid.	Acid equiv.	N (found), %.
2-Carboxy-	—	0·13	0·4	207—208°(d.)	232, 232	12·3
3-Carboxy- ...	—	—	2·5	269°(d.)	223, 226	12·7
4-Carboxy-	0·61	1·51	0·9	236—237°(d.)	224, 238	12·5
4-Carbethoxy-...	0·68	1·37	1·61	236—237°(d.)	224, 238	12·5

$C_{13}H_{12}O_2N_2$ requires N, 12·3%; equiv., 228. $C_{14}H_{12}O_4N_2$ requires N, 10·3%; equiv., 136.

Benzhydryl Ether of 4-Hydroxyazobenzene.—4-Hydroxyazobenzene (8·2 g.) was dissolved in dry benzene (160 ml.), and a solution of diphenyldiazomethane (9 g.) in benzene added. The solution was kept for 18 hours at 32° and then concentrated to 25 ml. The *ether* obtained (8·3 g.) crystallised from ethyl alcohol as yellow needles, m. p. 127° (Found : N, 8·0. $C_{25}H_{20}ON_2$ requires N, 7·7%).

UNIVERSITY OF MELBOURNE.

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194. *Optical Activity dependent on a Six-covalent Bivalent Osmium Complex.*

By F. H. BURSTALL, F. P. DWYER, and (MISS) E. C. GYARFAS.

The reaction between potassium osmichloride $K_2[OsCl_6]$ or ammonium osmibromide $(NH_4)_2[OsBr_6]$ and excess of 2 : 2′-dipyridyl at 260—280° yields the complexes [Os $Cl_2$2dipy]Cl,$3H_2O$ and [Os 3dipy]Cl_2,$6H_2O$ and the corresponding bromides after separation and crystallisation from water. The dark-green bivalent osmium complex is stable towards aqueous acids and alkalis and has been converted into the corresponding *iodide*, *perchlorate*, and *hydroxide*. By use of silver antimonyl tartrate optically active enantiomorphs of the *antimonyl tartrate* and the *iodide* have been obtained.

IT was shown some years ago by one of us (Burstall, *J.*, 1936, 173) that 2 : 2′-dipyridyl and ruthenium trichloride gave the well-defined stable salt [Ru 3dipy]Cl_2,$6H_2O$. The cation of this complex salt was sufficiently stable to be resolved into optically active forms by use of ammonium (+)- and (−)-tartrate. It has now been found that reaction of 2 : 2′-dipyridyl and potassium osmichloride and ammonium osmibromide at 260—280° results in reduction of the quadrivalent osmium salts to the tervalent and bivalent states with concurrent formation of the *chlorides* [OsCl_2 2dipy]Cl,$3H_2O$ (I) and [Os 3dipy]Cl_2,$6H_2O$ (II) or the corresponding *bromides*. The reactions of potassium osmichloride and ammonium osmibromide with 2 : 2′-dipyridyl are not, however, identical; the former gives a mixture of (I) and (II), except in presence of metallic osmium or other reducing agents which lead to (II) alone, whereas ammonium osmibromide gives almost entirely the bivalent osmium salt most conveniently isolated as the *iodide* [Os 3dipy]I_2,$3H_2O$ (III).

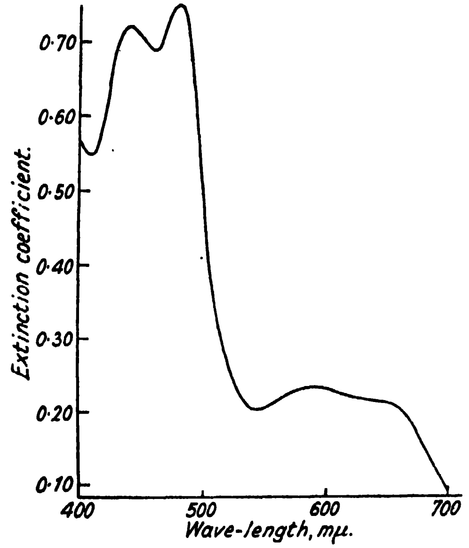
The dark red tervalent chloride (I) has not been closely examined but it can be reduced to (II) by heating it with 2 : 2′-dipyridyl and osmium metal. The chloride (II) and other salts of the complex cation [Os 3dipy]$^{++}$ are very dark green, crystalline substances which give intensely coloured solutions, very dark green by reflected light and dark red by transmitted light, even at concentrations of 10^{-6}M. The complex ion is stable in strongly acid or alkaline solutions, but in nitric acid or concentrated sulphuric acid the colour changes to red, probably by oxidation, with formation of a tervalent osmium complex ion of the type [Os 3dipy]$^{+++}$. Oxidation is accomplished by reagents such as ceric sulphate. The complex ion acts as a reversible redox indicator, the reaction

$$[\text{Os 3dipy}]^{++}\ (\text{green}) \longrightarrow [\text{Os 3dipy}]^{+++}\ (\text{red}) + e^-$$

having a potential of approximately 1 volt.

The separation of the optically active forms of the iodide [Os 3dipy]I_2,$3H_2O$ was carried out through the corresponding *antimonyl tartrate* but could be achieved, although less effectively, through the (+)-*tartrate* as with the analogous ruthenium derivative. The optically active antimonyl tartrates [Os 3dipy]$(SbOC_4H_4O_6)_2,2H_2O$, the less soluble being the lævorotatory salt, α^{20}_{5461} −0·08° in 0·0053% solution, $[\alpha]^{20}_{5461} \sim -1500°$, were converted into the iodides by potassium iodide and crystallised to constant rotation, the active forms separating in the least soluble portions during crystallisation. The observed rotations in 0·004% solutions of [Os 3dipy]I_2,H_2O were +0·085° and −0·09°, hence $[\alpha]^{20}_{5461}$ are about +2100° and −2200° respectively. These figures correspond to molecular rotations of the order of ±21,000°. Although optical activity is manifested in mercury light (λ 5461), the solutions do not show rotation in Na_D light, the wave-length of which is close to an absorption maximum (see Figure) for these solutions. The complex osmium iodide clearly has an abnormal rotatory dispersion, and an investigation of this effect with this salt and the corresponding ruthenium, iron, and nickel complexes is at present being carried out by two of the authors (F. P. D. and E. C. G.). It should also be noted that oxidation of the optically active ion [Os 3dipy]$^{++}$ to the tervalent condition [Os 3dipy^{+++}] does not destroy the activity; moreover, the original activity is regained on reduction to the bivalent complex.

Absorption spectrum of Os(dipy)$_3$I$_2$,3H$_2$O
(c = 5·5 × 10^{-5}M.).



The optical resolution of this bivalent osmium salt is the first recorded resolution of an osmium compound in any valency state.

EXPERIMENTAL.

Dichlorobis-2 : 2′-dipyridylosmium(III) *Chloride Trihydrate* (I).—An intimate mixture of potassium osmichloride (1 g.) and 2 : 2′-dipyridyl (5 g.) was heated and stirred at 260° for 1 hour. The cold dark brown solid was then extracted with benzene to remove excess of 2 : 2′-dipyridyl. The insoluble portion was leached with warm water until no more solid dissolved, and filtered from a brown microcrystalline residue which was not further studied. The aqueous filtrate was evaporated and cooled; red needles of the complex *chloride* then separated. After crystallisation from water this was air-dried (Found : Os, 28·7; Cl, 15·8; H_2O, 8·4. $C_{20}H_{16}N_4Cl_3Os,3H_2O$ requires Os, 28·7; Cl, 16·1; H_2O, 8·1%). A solution of this chloride in water or alcohol was decomposed by aqueous alkalis with separation of a black hydrated osmium oxide but was not altered by being heated with 2N-hydrochloric acid. With a large excess of ammonium (+)-tartrate, the chloride gave an unstable complex tartrate which gave only optically inactive preparations on regeneration of the chloride with ammonium chloride or hydrochloric acid. Aqueous potassium iodide and sodium nitrite gave crystalline sparingly soluble salts with strong solutions of the chloride.

Tris-2 : 2′-dipyridylosmium(II) *Chloride Hexahydrate* (II).—(*a*) The filtrate after separation of the red chloride (I) was made alkaline with 2N-sodium hydroxide, boiled for a few minutes to decompose tervalent salt, cooled, filtered from a black deposit of hydrated osmium oxide, acidified with hydrochloric acid, and evaporated to dryness. The green chloride was extracted with alcohol, the extract was evaporated, and the residue crystallised from a small quantity of water, to give lustrous dark green leaflets of the chloride (II).

(*b*) Potassium osmichloride or the tervalent salt (I) (0·5 g.), metallic osmium (0·1 g.), and 2 : 2′-dipyridyl were heated at 270° for 1 hour. After removal of excess of 2 : 2′-dipyridyl the residue was extracted with water, and the filtered solution was treated as described in (*a*).

(*c*) A solution of the complex iodide (see below) was triturated with an excess of freshly prepared silver chloride and then filtered, and the resulting dark green solution evaporated to dryness and dried over calcium chloride (Found : N, 10·1, 10·1; Cl, 8·8; Os, 23·0, 22·4; H_2O, 13·1. $C_{30}H_{24}N_6Cl_2Os,6H_2O$ requires N, 10·0; Cl, 8·5; Os, 22·7; H_2O, 13·0%). This *chloride* was easily soluble in water or alcohol but insoluble in ether or benzene.

Tris-2 : 2′-dipyridylosmium(II) *Bromide Trihydrate.*—This salt was obtained by (*a*) treating the chloride (II) with excess of freshly prepared silver oxide, filtering, and adding hydrobromic acid, (*b*) adding a concentrated solution of potassium bromide to a strong solution of the chloride (II), or (*c*) triturating the corresponding iodide with silver bromide, filtering, and evaporating the solution. This *bromide* which formed dark green hexagonal plates was dried over calcium chloride (Found : N, 9·8, 9·8, 9·9; Br, 18·3; Os, 21·5. $C_{30}H_{24}N_6Br_2Os,3H_2O$ requires N, 9·6; Br, 18·3; Os, 21·8%). It was slightly less soluble in water than was the corresponding chloride, but was otherwise similar.

Tris-2 : 2′-dipyridylosmium(II) *Iodide Trihydrate.*—Ammonium osmibromide (1·0 g.) and 2 : 2′-dipyridyl (2·0 g.) were mixed intimately and heated carefully in a test-tube until the base in the mixture melted and then became red. The test-tube was loosely stoppered and transferred to an oil-bath at 270—280° for 1 hour; a dark green, almost black product and an almost colourless liquid then remained.

The liquid consisting mainly of unchanged 2 : 2′-dipyridyl was decanted and the solid extracted with hot water (200 ml.). After filtration from traces of a dark insoluble material, the salts in solution were fractionally precipitated with aqueous potassium iodide. The first fraction consisted of a red salt which was not further studied, whereas the more soluble fractions consisted of nearly pure tris-2 : 2′-dipyridylosmium(II) iodide trihydrate which was washed with ice-water and crystallised from hot water with addition of potassium iodide. The complex *iodide*, which has also been made by adding potassium iodide to a solution of the corresponding chloride, formed almost black, lustrous monoclinic prisms and was dried over calcium chloride (Found: N, 8·8; I, 26·9, 26·3; Os, 19·5. $C_{30}H_{24}N_6I_2Os,3H_2O$ requires N, 8·8; I, 26·3; Os, 19·8%).

Tris-2 : 2′-dipyridylosmium(II) *Perchlorate Monohydrate.*—This *salt* separated, on addition of sodium perchlorate solution to a hot solution of the corresponding iodide, as a sparingly soluble microcrystalline deposit (Found: N, 9·6; Os, 21·4. $C_{30}H_{24}N_6O_8Cl_2Os,H_2O$ requires N, 9·6; Os, 21·7%).

Tris-2 : 2′-dipyridylosmium(II) *Hydroxide Octahydrate.*—This compound was prepared from the corresponding iodide and freshly prepared silver oxide. The mixture was filtered and evaporated to dryness over solid sodium hydroxide. The crystalline *base* was deliquescent and absorbed carbon dioxide from the air (Found: N, 10·0. $C_{30}H_{26}O_2N_6Os,8H_2O$ requires N, 10·1%). Solutions of this hydroxide liberate ammonia from ammonium salts and precipitate ferric and cupric hydroxides from solution.

Optical Activity of Bivalent Osmium Salts.—(1-Dm. tubes were used in all determinations of rotation.) (−)-*Tris-2 : 2′-dipyridylosmium*(II) *antimonyl* (+)-*tartrate dihydrate.* The racemic iodide [Os 3dipy]I_2,$3H_2O$ (2·0 g.) in hot water (150 ml.) was shaken with silver antimonyl (+)-tartrate (0·8 g.) for 10 minutes and the solution was then filtered. The filtrate was concentrated on a steam-bath until about half the salt in solution could be crystallised by cooling in ice. The crystals of the *tartrate* were separated and washed with small quantities of ice-cold alcohol to remove traces of the more soluble salts (Found: N, 6·6; Os, 15·0. $C_{38}H_{32}O_{14}N_6Sb_2Os,2H_2O$ requires N, 6·65; Os, 15·0%). A 0·0053% solution in water gave α^{20}_{5461} −0·08°.

(−)-*Tris-2 : 2′-dipyridylosmium*(II) *iodide trihydrate.* The foregoing antimonyl tartrate was dissolved in warm water and fractionally precipitated with potassium iodide solution. With the exception of the final fraction, which was slightly lævorotatory, all fractions were strongly active. These fractions were crystallised from water to constant rotation, racemate being left in the filtrates. The lævorotatory *iodide* formed flat micaceous plates (Found: N, 8·8; I, 26·4. $C_{30}H_{24}N_6I_2Os,3H_2O$ requires N, 8·7; I, 26·3%) which in 0·004% solution in water gave α^{20}_{5461} (mean) −0·09°.

(+)-*Tris-2 : 2′-dipyridylosmium*(II) *iodide trihydrate.* The filtrate from the preparation of the antimonyl tartrate was diluted with water to 120 ml., heated to 60°, and fractionally precipitated with aqueous potassium iodide. The less soluble fractions, which were strongly dextrorotatory, were crystallised several times from water with addition of potassium iodide and formed micaceous crystals of the dextrorotatory *iodide* (Found: N, 8·7; I, 26·0. $C_{30}H_{24}N_6I_2Os,3H_2O$ requires N, 8·7; I, 26·3%). A 0·004% solution in water gave α^{20}_{5461} (mean) +0·085°.

(+)-*Tris-2 : 2′-dipyridylosmium*(II) (+)-*tartrate trihydrate.* A solution of 0·3 g. of the chloride [Os 3dipy]Cl_2,$6H_2O$ in water (10 ml.) was cooled to 0° and treated with solid ammonium (+)-tartrate (5 g.); the tartrate of the dextrorotatory complex separated in lustrous plates. These were freed from liquid between filter paper and dried by being washed with acetone. The solid was dissolved in alcohol to separate ammonium tartrate, filtered, diluted with a few drops of water, and precipitated by addition of acetone. This *tartrate* was micro-crystalline (Found: N, 9·7; Os, 21·6. $C_{34}H_{28}O_6N_6Os,3H_2O$ requires N, 9·8; Os, 22·1%). A 0·005% solution gave α^{20}_{5461} +0·1°. A dextrorotatory iodide and bromide can be produced from this tartrate by addition of potassium bromide or iodide; lævorotatory salts can also be isolated from the mother-liquors after separation of the dextrorotatory tartrate.

Analyses.—The analyses of the compounds for carbon and hydrogen were unsatisfactory owing to deposition of osmium in the absorption tubes. Halogen was determined by the distillation method (Dwyer and Nyholm, *J. Proc. Roy. Soc., New South Wales*, 1941, **75**, 127), nitrogen by the combustion method (Dumas), and osmium by a colorimetric procedure which will be recorded elsewhere (Dwyer and Gibson).

The work, carried out at the Chemical Research Laboratory (1935—1936), formed part of the programme of the Chemistry Research Board and is published by permission of the Director. The authors are indebted to Dr. F. Lions for 2 : 2′-dipyridyl and one of them (E. C. G.) thanks the Research Committee of the University of Sydney for a Research Assistantship.

CHEMICAL RESEARCH LABORATORY, TEDDINGTON, MIDDLESEX.
UNIVERSITY OF SYDNEY, SYDNEY, N.S.W., AUSTRALIA.
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195. *Diterpenes. Part III. The Diterpenes from* Podocarpus ferrugineus.

By LINDSAY H. BRIGGS, R. W. CAWLEY, J. A. LOE, and W. I. TAYLOR.

The diterpene fraction of the essential oil of *Podocarpus ferrugineus* has been found to contain (+)-phyllocladene, (+)-kaurene, and a new dextrorotatory isomer, m. p. 59—60°. A re-examination of crude "mirene" and "mirene hydrochloride" (Hosking and Short, *Rec. Trav. chim.*, 1928, **47**, 834) showed them to contain phyllocladene and kaurene hydrochloride, respectively. It is evident that "mirene" was not homogeneous, and was probably impure *iso*phyllocladene. The name mirene has been transferred to the new isomer.

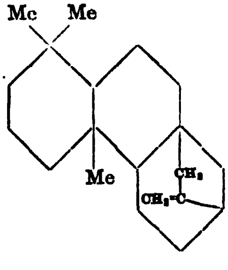
FROM the essential oil of *Podocarpus ferrugineus* ("miro") Hosking and Short (*Rec. Trav. chim.*, 1928, **47**, 834) isolated an apparently new diterpene, mirene, m. p. 102—104°, $[\alpha]^{15}_{5461}$

+27·15°,* forming a monohydrochloride, m. p. 97—98°, from which the hydrocarbon was regenerated on treatment with alcoholic potassium hyroxide, and a dihydro-derivative, m. p. 73—74° (Hosking, *Rec. Trav. chim.*, 1930, **49**, 1036). Following an observation by one of us (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) that the m. p. of dihydromirene was the same as that of α-dihydrophyllocladene, suggesting a relationship between mirene and phyllocladene, samples of mirene hydrochloride and dihydromirene were submitted by Dr. J. R. Hosking to Mr. C. W. Brandt with the suggestion that they would prove identical with phyllocladene hydrochloride and α-dihydrophyllocladene, respectively. No depressions in m. p. were observed (Brandt, *New Zealand J. Sci. Tech.*, 1938, **20**, 8B) thus confirming the suggestion. Brandt also obtained a hydrocarbon, m. p. 103°, by treating the hydrochloride with alcoholic potassium hydroxide, which did not depress the m. p. of *iso*phyllocladene. His regenerated hydrocarbon was reported as lævorotatory, however, whereas *iso*phyllocladene is dextrorotatory, and from our experience in the kaurene series a strong depression should have been observed with the enantiomorphs. Brandt, however, in a private communication, has informed us that the rotation of his regenerated hydrocarbon was done on a micro-scale, and he would not insist that the rotation was negative under the experimental conditions.

It would appear therefore that mirene is an impure form of *iso*phyllocladene, the purest specimen of which has m. p. 112° (Briggs and Sutherland, *J. Org. Chem.*, 1942, **7**, 397).

With the kind permission of the late Dr. J. R. Hosking we have continued the investigation of the diterpene fraction of the essential oil of this species. In contrast with the results of Hosking and Short we have isolated, by fractional crystallisation, three diterpenes, (+)-phyllocladene, identified by mixed m. p. and Debye–Scherer patterns, (+)-kaurene, identified by Debye–Scherer patterns and conversion into (+)-*iso*kaurene, and a new diterpene, m. p. 59—60°, $[\alpha]_D^{20}$ +43·8° (monohydrochloride, m. p. 82°, and dihydro-derivative, m. p. 63—64°). Since the original mirene from this oil has been shown to be *iso*phyllocladene, we have transferred the name mirene to the new isomer. Like rimuene (McDowall and Finlay, *J. Soc. Chem. Ind.*, 1925, **44**, 42T), phyllocladene (Aitken, *J. Soc. Chem. Ind.*, 1928, **47**, 223T), and cupressene (Briggs and Sutherland, *loc. cit.*), mirene is isomerised by glacial acetic acid into *iso*phyllocladene. Mirene gives a strong m. p. depression when mixed with rimuene and its Debye–Scherer pattern shows that it is neither identical with nor an enantiomorph of α-cryptomerene from *Cryptomeria japonica* (Uchida, *Bull. Forest Expt. Stat. Meguro, Tokyo*, 1915, Reprint) for a sample of which we are greatly indebted to Professor Uchida.

Through the courtesy of Professor L. Ruzicka, to whom we are greatly indebted, we have been able to re-examine some of the original material of Hosking and Short. A sample of "crude mirene," m. p. 60—70°, on crystallisation afforded (+)-phyllocladene, identified through mixed m. p., rotation, and conversion into *iso*phyllocladene and α-dihydrophillocladene. On the other hand, a sample of "mirene hydrochloride," m. p. 94°, yielded (+)-kaurene hydrochloride, m. p. 116°, on crystallisation, identified through its m. p., rotation, and conversion into (+)-*iso*kaurene, undepressed in m. p. by an authentic specimen. With the small amount of material at our disposal it was not possible to examine the mother liquors for mirene.



Brandt [already reported by one of us (Briggs, *Proc. Roy. Soc. New South Wales*, 1947, **80**, 154)] has adduced evidence for the inset structure for phyllocladene. Four stable geometrical isomerides of this structure may occur, each in (+)- and (−)-forms, and it would appear that a number of naturally occurring diterpenes are stereoisomers of the same general pattern.

Kaurene is isomerised by boiling glacial acetic acid into *iso*kaurene but with boiling alcoholic sulphuric acid it is converted into the γ-isomer, m. p. 196—198°, reported by Nishida and Uoda (*Bull. Agric. Soc. Japan*, 1930, **1**, Nos. 1—3), under conditions which left *iso*phyllocladene unchanged. *iso*Kaurene does not depress the m. p. of kaurene and forms a eutectic containing 60% kaurene and 40% *iso*kaurene.

EXPERIMENTAL.

The leaves and terminal branchlets of *Podocarpus ferrugineus* (140 lb.), collected at Mangapehi in June through the courtesy of Mr. G. R. Hammond, State Forest Service, to whom we are greatly indebted, produced 95 g. (0·15% yield) of a pale yellow oil on steam distillation. The oil was distilled in a Bower and Cooke type of column (*Ind. Eng. Chem. Anal.*, 1943, **15**, 290), the lower terpene fractions at 20 mm. and the higher fractions at 3·5 mm., the bath temperature not rising above 215° at any stage. No attempt was made to separate the constituents below the diterpene fraction. The following major fractions were obtained :

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* The lævorotation of mirene reported by one of us (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) and Brandt (*New Zealand J. Sci. Tech.*, 1938, **20**, 8B) is an error.

Fraction.	B. p.	n_D^{25}.	Wt., g.
I	<47°/20 mm.	1·464	37·8
II	45—125/3·5 mm.	1·464 ~ 1·492	11·3
III	130—160/3·5 mm.	1·514	13·0

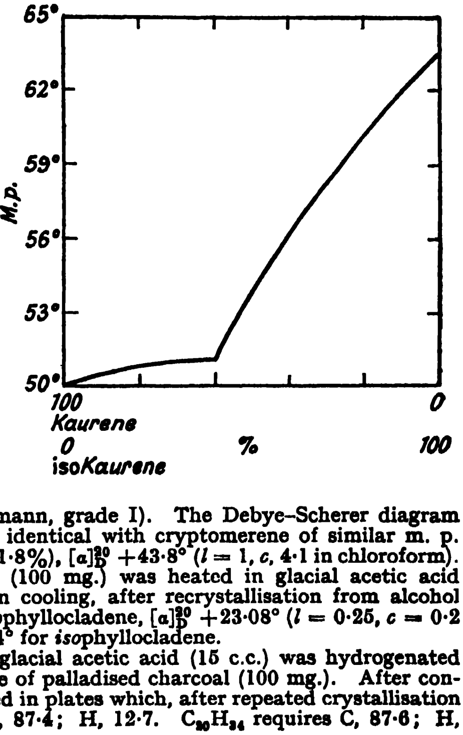
The residual brown oil (45 g.) solidified (m. p. *ca.* 40—45°) and was investigated for diterpenes.

Separation of this material into three constituents was only achieved by a long series of systematic fractional crystallisations from ethyl acetate and both alcohol and absolute alcohol. Coloured material which hindered crystallisation was removed at certain stages by chromatographing solutions in light petroleum through a 20 × 1 cm. column of alumina. By this means the following constituents were obtained.

(+)-*Phyllocladene.*—The small amount of pure material (<400 mg.) had m. p. and mixed m. p. with authentic (+)-phyllocladene (from *Araucaria excelsa*) 96°, whilst the Debye–Scherer diagrams were identical.

(+)-*Kaurene.*—Only 1·1 g. were obtained in a pure state; it had m. p. 49° and $[\alpha]_D^{20}$ +101° (l = 1; c, 1·5 in chloroform). It gave a m. p. depression when mixed with (—)-kaurene (from *Agathis australis*) but the Debye–Scherer diagrams were identical.

A sample of the diterpene isolated from the essential oil of *Podocarpus spicatus* by Butler and Holloway (*J. Soc. Chem. Ind.*, 1939, **58**, 223) was kindly sent to us for comparison. It proved to be lævorotatory whilst the Debye–Scherer diagram indicated that it was mixture of kaurene and *iso*kaurene.



The melting-point diagram for mixtures of kaurene and *iso*kaurene, showing a eutectic at 40% kaurene + 60% *iso*kaurene, is given in the figure.

Isomerisation of Kaurene.—(a) *With glacial acetic acid.* (—)-Kaurene (100 mg., from *Agathis australis*), dissolved in glacial acetic acid (6 c.c.), was gently heated under reflux for 1¼ hours. The product separating on cooling, after repeated crystallisation from alcohol, formed plates, m. p. and mixed m. p. with (—)-*iso*kaurene 64°. The enantiomorph, of the same m. p., was similarly obtained from (+)-kaurene.

(b) *With alcoholic sulphuric acid.* (—)-Kaurene (100 mg.), dissolved in alcohol (9 c.c.) and concentrated sulphuric acid (3 drops), was heated under reflux for 6½ hours. The material separating on cooling was crystallised repeatedly from alcohol and then formed prismatic needles, m. p. 196—198° [Found: M (micro-Rast), 266, 268. Calc. for $C_{20}H_{32}$: M, 272].

Mirene.—This is apparently the diterpene occurring in the greatest amount, and 3·2 g. of pure material were obtained. No alteration in m. p. could be achieved by repeated crystallisation from ethyl acetate or alcohol from which *mirene* separated in rectangular plates, or in any fraction after chromatographing the solution through a 20-cm. column of alumina (Brockmann, grade I). The Debye–Scherer diagram also indicated homogeneity and proved that it was not identical with cryptomerene of similar m. p. (Found : C, 88·5; H, 12·3. $C_{20}H_{32}$ requires C, 88·2; H, 11·8%), $[\alpha]_D^{20}$ +43·8° (l = 1, c, 4·1 in chloroform).

Isomerisation of mirene to iso*phyllocladene.* Mirene (100 mg.) was heated in glacial acetic acid solution (10 c.c.) for 6 hours. The solid separating on cooling, after recrystallisation from alcohol (charcoal), formed needles, m. p. 110°, undepressed by *iso*phyllocladene, $[\alpha]_D^{20}$ +23·08° (l = 0·25, c = 0·2 in chloroform). Briggs (*J.*, 1937, 79) records $[\alpha]_D^{17}$ +23·4° for *iso*phyllocladene.

Dihydromirene. A solution of mirene (100 mg.) in glacial acetic acid (15 c.c.) was hydrogenated at 34 lb. per sq. in. pressure for 16 hours in the presence of palladised charcoal (100 mg.). After concentration of the filtered solution, *dihydromirene* separated in plates which, after repeated crystallisation from glacial acetic acid, had m. p. 63—64° (Found : C, 87·4; H, 12·7. $C_{20}H_{34}$ requires C, 87·6; H, 12·4%).

Mirene hydrochloride. Dry hydrogen chloride was passed through a solution of mirene (100 mg.) in glacial acetic acid (2 c.c.) and dry ether (0·5 c.c.) cooled in ice. The colourless solid which formed was washed with glacial acetic acid and ethyl acetate and recrystallised from ethyl acetate to a constant m. p. The *hydrochloride* had m. p. 82°, $[\alpha]_D^{15}$ +59·9° (l = 1; c, 0·4 in chloroform) (Found : Cl, 12·0. $C_{20}H_{32}$,HCl requires Cl, 11·5%).

Re-examination of Hosking and Short's Material.—Isolation of phyllocladene. A sample (450 mg.) of Hosking and Short's material, labelled " crude mirene," had m. p. 60—70°. On crystallisation from absolute alcohol this formed plates, m. p. 91—93° (yield, 400 mg.), raised by further crystallisation to m. p. 95—96° (yield, 300 mg.) and two further crystallisations to a constant m. p. 96—97°, undepressed by authentic (+)-phyllocladene, $[\alpha]_D^{16}$ +15·5° ± 2° (l = 1; c, 2·27 in chloroform).

The purified material (40 mg.) was heated under reflux with alcoholic sulphuric acid (2 c.c.; 10% solution) for ½ hour. The plates separating on cooling, after recrystallisation from absolute alcohol, formed needles, m. p. 111—112°, undepressed by authentic (+)-*iso*phyllocladene, $[\alpha]_D^{16}$ +23·5° ± 2° (l = 1; c, 1·92 in chloroform).

The purified material (60 mg.) was hydrogenated in glacial acetic acid solution in the presence of platinum oxide. Concentration of the filtered solution afforded needles, which, after recrystallisation from the same solvent, had m. p. 70—71°, undepressed by an authentic sample of (+)-α-dihydrophyllocladene (Found: C, 87·1; H, 12·4. Calc. for $C_{20}H_{34}$: C, 87·5; H, 12·5%), $[\alpha]_D^{13}$ +21° ± 2° (*l* = 1; *c*, 1·12 in chloroform).

Isolation of kaurene derivatives. A sample of Hosking and Short's "mirene hydrochloride" had m. p. 94°, raised to 115—116° by a single crystallisation from ethyl acetate and to 116° by a further crystallisation (Found: C, 77·7; H, 10·9. Calc. for $C_{20}H_{33}$,HCl: C, 77·8; H, 10·8%), $[\alpha]_D^{21}$ +38·5° ± 1° (*l* = 1; *c*, 2·0 in chloroform). In Part I (*J.*, 1948, 1888) values of m. p. 114—115° and $[\alpha]_D^{20}$ −40·0° are recorded for (−)-kaurene hydrochloride.

The hydrochloride (100 mg.) was heated under reflux with alcoholic sodium hydroxide (5 c.c.; 3% solution) for 3 hours. After addition of water, the diterpene was extracted with chloroform and repeatedly crystallised from absolute alcohol, from which it separated in plates or needles, m. p. 64—65°, undepressed by authentic (+)-*iso*kaurene (Found: C, 88·0; H, 11·7. Calc. for $C_{20}H_{32}$: C, 88·2; H, 11·8%), $[\alpha]_D^{21}$ +31° ± 2° (*l* = 1; *c*, 1·79 in chloroform). In Part I (*loc. cit.*) a value of $[\alpha]_D^{20}$ −25·9° is recorded for (−)-*iso*kaurene.

The analyses are by Drs. Weiler and Strauss, Oxford, Mr. Manser, Zürich, and Mr. Seelye of this department.

We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, and the Royal Society of New Zealand for grants, and to Mr. L. D. Calvert for the *X*-ray powder photographs. One of us (W. I. T.) is grateful for a National Research Scholarship.

AUCKLAND, UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND.
EIDG. TECHNISCHEN HOCHSCHULE, ZÜRICH, SWITZERLAND.

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196. *Diterpenes. Part IV. The Isolation of Phyllocladene from the Essential Oil of* Podocarpus spicatus *Grown in the North Island of New Zealand.*

By LINDSAY H. BRIGGS and J. A. LOE.

Phyllocladene has been isolated as the only solid diterpene from the essential oil of *Podocarpus spicatus* grown in the North Island of New Zealand, whereas that grown in the South Island yields kaurene (cf. Butler and Holloway, *J. Soc. Chem. Ind.*, 1939, 58, 223).

FROM the essential oil of *Podocarpus spicatus* growing in the South Island of New Zealand Butler and Holloway (*J. Soc. Chem. Ind.*, 1939, **58**, 223) isolated a diterpene which they suggested was kaurene [cf. Part I (*J.*, 1948, 1888) for the identification of podocarpene with kaurene] without definitely claiming its identity. From the evidence submitted in Part III (preceding paper) it is clear that they isolated the lævo-isomer. Seeking a better source of kaurene [a yield of only 1·2% was obtained from the essential oil of *Agathis australis* (Part I, *loc. cit.*) whereas Butler and Holloway record a yield of 25% from the oil of *Podocarpus spicatus*], we have examined the essential oil of *P. spicatus* grown in the centre of the North Island of New Zealand. Although a thorough search, by careful fractionation followed by chromatography, was made for different diterpenes, particularly kaurene, the only diterpene isolated was phyllocladene in very small yield.

Wide variation in the percentage of constituents and also in the type of compounds present in species of plants, morphologically indistinguishable, has frequently been observed in the Australian flora but this is the first record from New Zealand.

The essential oil of *Podocarpus totara* contains rimuene and possibly a liquid diterpene, totarene (Aitken, *J. Soc. Chem. Ind.*, 1929, **48**, 344T; Beath, *ibid.*, 1933, **52**, 338T). The isolation of phyllocladene from the leaf-oil of "*P. hallii*," considered by botanists to be a variety of *P. totara* and not a separate species led one of us (Briggs, *Proc. Roy. Soc. New Zealand*, 1941, **70**, 173) to the suggestion that this fact would support the classification of *P. hallii* as a true species and not a variety. The above evidence from *P. spicatus* weakens the case for such a suggestion.

An unusual constituent, a liquid *olefin*, $[CH_2]_n$, b.p. 130—135°/0·01 mm., was isolated from the diterpene portion of the oil.

EXPERIMENTAL.

The leaves and terminal branchlets of *Podocarpus spicatus* (832 lbs.) collected from the Pureora Forest, Mangapehi, through the courtesy of Mr. G. R. Hammond, State Forest Service, to whom we are greatly indebted, produced, on steam distillation for 16—18 hours, 477 g. (0·13% yield) of pale yellow oil. The oil was then distilled through a column of the type described by Dostrovsky and Hughes (*Nature*, 1946, **158**, 164), the terpene fraction (279 g.) at 10 mm. and the oxygenated terpenes and sesquiterpene fraction

(89 g.) at 5 mm. The temperature of the still-pot did not exceed 140° at any stage. The residual oil was transferred to a modified Craig column (*Ind. Eng. Chem. Anal.*, 1937, **9**, 441), 20 cm. long, without condenser and with a side arm dipping into a series of receivers, and was distilled at 0·01 mm. The first yellowish-green fraction (33·8 g.), b. p. 66—97°/0·01 mm., n_D^{25} 1·5056 ~ 1·5057, consisted of sesquiterpene alcohols whilst the remaining fractions: *A*, greenish-blue (3·82 g.), b. p. 111—122°/0·01 mm., n_D^{25} 1·5059; *B*, greenish blue (3·52 g.), b. p. 122—129°/0·01 mm., n_D^{25} 1·5102; *C*, blue (8·95 g.), b. p. 129—145°/0·01 mm., n_D^{25} 1·5173; *D*, blue (2·90 g.), b. p. 130—140°/0·01 mm., n_D^{25} 1·5177; and the residue (24·5 g.) were investigated for diterpenes.

Fractions *A* and *B* were dissolved in dry light petroleum (10 c.c.), chromatographed on a 18 × 1·5 cm. column of alumina (Brockmann, grade I), and eluted with light petroleum and finally with light petroleum containing1% methyl alcohol. Six fractions, each of *ca.* 10 c.c., were collected in each case, and the solvent was removed and the residual oils were kept dry in the refrigerator. No solid separated from any of these fractions.

A part of fraction *C* (1·89 g.) was similarly treated and gave the following fractions (all colourless):

Fraction	*C*1	*C*2	*C*3	*C*4	*C*5—*C*10
n_D^{25}	1·5100	1·5158	1·5174	1·5205	—
Weight (g.)	0·01	0·81	0·51	0·30	0·03

From *C*2 a solid separated (12 mg.) which, after recrystallisation from alcohol, had m. p. 95°, undepressed by a specimen of phyllocladene. A trial experiment showed that phyllocladene was not isomerised on chromatography as above.

Fraction *C*4 was distilled in a Craig micro-column and gave an oil, b. p. 130—135°/0·01 mm., n_D^{24} 1·5202, d_4^{19} 0·9718 (determined in a micro-pyknometer similar to that described by Clemo and McQuillen, *J.*, 1935, 1220), $[\alpha]_D^{21}$ + 39·73° (l = 1, c = 0·8 in chloroform) (Found: C, 85·9; H, 14·2. $[CH_2]_n$ requires C, 85·7; H, 14·3%). The *hydrocarbon* decolorised a solution of bromine in chloroform and gave a brown coloration with tetranitromethane.

From the main bulk of fraction *C* a colourless solid separated which, after recrystallisation from alcohol, had $[\alpha]_D^{20}$ + 14·99° (l = 1, c = 2·1 in chloroform) and m. p. 96°, undepressed by phyllocladene. Briggs (*J.*, 1937, 79) records $[\alpha]_D^{25}$ + 15·8° for phyllocladene. The material, after isomerisation with sulphuric acid in alcoholic solution (Briggs, *loc. cit.*) and crystallisation from methyl alcohol, had m. p. 109—110°, undepressed by a specimen of *iso*phyllocladene.

The solid separating from fraction *D* was also proved to be phyllocladene by mixed m. p. and rotation, $[\alpha]_D^{20}$ + 15·62° (l = 1, c = 0·3 in chloroform).

The residue was only partly soluble in hot alcohol from which solution there separated on storage 2 g. of crystalline material which was proved to be phyllocladene by mixed m. p.

The analysis is by Mr. Seelye of this department.

We are indebted to the Chemical Society, the Royal Society of New Zealand, and the Australian and New Zealand Association for the Advancement of Science for grants.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, November 24th*, 1949.]

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197. *The Preparation of a Series of* (±)-n-*Eicosanols and* n-*Eicosanones.*

By VIVIENNE R. CHURCHWARD, N. A. GIBSON, R. J. MEAKINS, and JOAN W. MULLEY.

The preparation and properties of the (±)-*n*-eicosanols ($C_{20}H_{42}O$) and *n*-eicosanones ($C_{20}H_{40}O$) having the polar groups in the 2-, 4-, 6-, 8-, and the 10-position are described.

IN the course of a programme of research into the dielectric properties of long-chain alcohols (Meakins and Sack, *Nature*, 1949, **164**, 798) and ketones (Meakins, *Nature*, 1948, **162**, 994; 1949, **163**, 840) it was desired to determine the effect of varying the position of the polar group in a normal paraffin chain. Eicos-2-,-4-,-6-,-8- and -10-ol and -one now described were prepared for that purpose. Of these compounds, only the *n*-eicosan-2-ol and *n*-eicosan-2-one have been reported previously (Pangborn and Anderson, *J. Amer. Chem. Soc.*, 1936, **58**, 10; Morgan and Holmes, *J. Soc. Chem. Ind.*, 1925, **44**, 108; Stenhagen and Stenhagen, *Arkiv Kemi., Mineral., Geol.*, 1945, **18**, *A*, No. 19).

The *n*-eicosanols were obtained by the Grignard reaction between alkylmagnesium iodides and the appropriate aldehydes, the product being separated from the hydrocarbon by-product by vacuum distillation, recrystallisation, or adsorption on alumina, according to chain-length. The yields varied from 20 to 55%, the higher yields being obtained with the alkyl halides of shorter chain-length. Pure, fresh-cut magnesium (99·95%) was used throughout.

EXPERIMENTAL.

(All m. p.s are uncorrected.)

(±)-n-*Eicosan*-2-ol.—The Grignard reagent was prepared from magnesium (9·5 g.), octadecyl iodide (119 g.), and ether (350 ml.), the mixture being heated under reflux during the addition of the iodide and for a further one hour. After the solution had cooled to room temperature, a solution of acetaldehyde (14 g.) in dry ether (15 ml.) was added slowly, with stirring. After being heated under reflux for a further 2 hours, the Grignard complex was decomposed with water (50 ml.), and 5N-hydrochloric acid (200 ml.) was added to dissolve the excess of magnesium. The ethereal layer was then separated, filtered to remove *n*-hexatriacontane, and washed with water, dilute sodium thiosulphate solution, and again several times with water, and dried (Na_2SO_4), and the ether distilled off.

The residual solid was dissolved in benzene and chromatographed on a column of alumina (1,100 g.), 5 cm. in diameter. Elution with benzene (1 l.) removed the hydrocarbon by-products and the crude (±)-*n*-eicosan-2-ol was then obtained by elution with ether. Recrystallisation from light petroleum gave a product (11·7 g.) in the form of well-defined crystalline plates, m. p. 59—60°. A portion of this was distilled under vacuum and the second of three fractions (b. p. 208—212°/7 mm.), having the smallest melting-point range, was recrystallised from alcohol. This gave (±)-*n*-eicosan-2-ol as a microcrystalline powder (well-defined plates from benzene), m. p. 58·5—59·0° (Lit., m. p. 52·0—52·7° for the (±)-compound; m. p. 62—63° for the (+)-form) (Found: C, 80·5, 80·3; H, 13·9, 13·8. Calc. for $C_{20}H_{42}O$: C, 80·5%; H, 14·1%).

(±)-n-*Eicosan-4-ol*.—This was similarly prepared from magnesium (2·5 g.) in dry ether (30 ml.), cetyl iodide (30 g.) in dry ether (50 ml.), and butyraldehyde (6·1 g.). The material obtained by elution of the chromatograph column with ether was recrystallised from light petroleum (b. p. 60—80°) then benzene, giving microcrystalline needles (7·7 g.), m. p. 54·0—54·5°. A portion of this product was distilled under vacuum and the second (b. p. 190—192°/3 mm.) of three fractions recrystallised from alcohol, giving (±)-n-*eicosan-4-ol* as microcrystalline needles (poorly defined), m. p. 55·0—55·3° (Found: C, 80·5, 80·5; H, 13·8, 13·9. $C_{20}H_{42}O$ requires C, 80·5; H, 14·1%).

(±)-n-*Eicosan-6-ol*.—This was prepared from magnesium (9·0 g.) in dry ether (200 ml.), tetradecyl iodide (100 g.) in dry ether (200 ml.), and hexanal (25·8 g.). The *n*-octacosane by-product was not precipitated, and was therefore contained in the solid mixture obtained by evaporation of the ether solution. This mixture was dissolved in light petroleum (b. p. 60—80°) and chromatographed on a column of alumina (1,500 g.), 5 cm. in diameter. Elution with light petroleum eliminated the hydrocarbons, and the eicosanol was then obtained by elution with benzene. Recrystallisation from light petroleum gave a product (24·1 g.), m. p. 55—57°, which was vacuum-distilled. The second fraction (b. p. 189°/2·7 mm.) was recrystallised from alcohol, giving (±)-n-*eicosan-6-ol* as a microcrystalline powder (needles from benzene), m. p. 57·7—57·8° (Found: C, 80·5, 80·5; H, 13·9, 13·8%).

(±)-n-*Eicosan-8-ol*.—The scale of the preparation was the same as that described for (±)-*n*-eicosan-6-ol. The mixture obtained from the ether solution was partly distilled under a vacuum to remove *n*-dodecane and the residue recrystallised from light petroleum (900 ml.; b. p. 60—80°), giving a product (62 g.), m. p. 57—59°. A portion of this was distilled under a vacuum and the second (b. p. 192°/3 mm.) of three fractions recrystallised from alcohol, giving (±)-n-*eicosan-8-ol* as microcrystalline plates (short needles from benzene), m. p. 57·7—57·9° (Found: C, 80·6, 80·4; H, 14·1, 13·8%).

(±)-n-*Eicosan-10-ol*.—The reaction product from the ether layer was recrystallised from light petroleum (500 ml.; b. p. 60—80°), giving a product, m. p. 62·5—64°. A portion of this was distilled under a vacuum and the second (b. p. 214°/7 mm.) of three fractions recrystallised from alcohol, giving (±)-n-*eicosan-10-ol* as microcrystalline plates (well-defined needles from benzene), m. p. 65·3—65·6° (Found: C, 80·5, 80·5; H, 14·0, 13·8%).

The Preparation of the n-*Eicosanones*.—A solution of the *n*-eicosanol (5 g.) in benzene (250 ml.) was added to a solution of sodium dichromate (7 g.) in acetic acid (5 ml.), sulphuric acid (9 ml.), and water (30 ml.), and the mixture shaken mechanically for 6 hours. The aqueous layer was removed, and the benzene layer washed with water, 0·5N-potassium hydroxide, and again several times with distilled water. The *n*-eicosanone was then obtained by evaporation of the benzene solution, and recrystallisation of the product twice from alcohol. The yield of pure product was, in each case, about 90%.

n-Eicosan-2-one formed crystalline flakes, m. p. 59·3—59·7° (lit. m. p. 58°) (Found: C, 81·0, 80·7; H, 13·5, 13·6; O, 5·6. Calc. for $C_{20}H_{40}O$: C, 81·1%; H, 13·5; O, 5·4%). 2 : 4-Dinitrophenylhydrazone: orange-yellow crystalline plates, m. p. 94·5—94·8°.

n-*Eicosan-4-one* was obtained as crystalline flakes, m. p. 54·0—54·5° (Found: C, 80·7, 80·8; H, 13·8, 14·0; O, 5·6%). 2 : 4-Dinitrophenylhydrazone: brick-red microcrystalline plates, m. p. 70·1—70·4°.

n-*Eicosan-6-one* formed crystalline flakes, m. p. 53·8—54·1° (Found: C, 81·4, 81·3; H, 13·8, 14·0; O, 5·6%). 2 : 4-Dinitrophenylhydrazone: yellow powder, m.p. 40·4—47·4°.

n-*Eicosan-8-one* formed crystalline flakes, m. p. 53·2—53·5° (Found: C, 81·0, 81·3; H, 13·8, 13·6; O, 5·7%). 2 : 4-Dinitrophenylhydrazone: yellow needles, m. p. 29·6—30·0°.

n-*Eicosan-10-one* was obtained as crystalline flakes, m. p. 53·7—54·0° (Found: C, 80·9, 81·0; H, 13·3, 13·4; O, 5·6%). The 2 : 4-dinitrophenylhydrazone was a yellow liquid at room temperature.

The work described formed part of the programme of the Division of Electrotechnology, Commonwealth Scientific and Industrial Research Organisation.

The authors thank Mr. R. Bradbury for the microanalyses.

DIVISION OF ELECTROTECHNOLOGY,
COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION,
AUSTRALIA.

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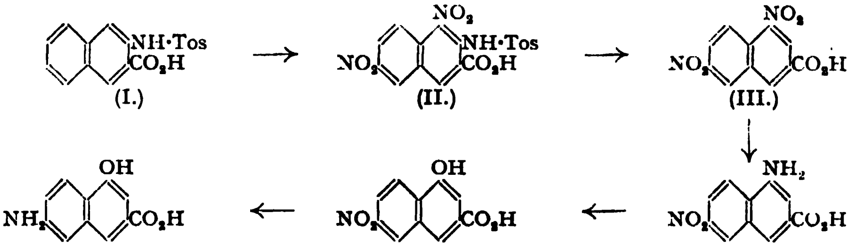
198. *Aminohydroxynaphthoic Acids. Part II. Attempted Synthesis of 7-Amino-4-hydroxy-2-naphthoic Acid ("Carboxy J-Acid") from 3-Amino-2-naphthoic Acid.*

By W. F. Beech and N. Legg.

A number of nitro- and bromo-derivatives of 3-amino-2-naphthoic acid have been prepared in an attempt to find a suitable route to 7-amino-4-hydroxy-2-naphthoic acid (IV). Poor yields of two suitable intermediates, 4 : 7-dinitro- and 4 : 7-dibromo-2-naphthoic acid, prevented their attempted conversion into the aminohydroxynaphthoic acid.

In Part I (*J.*, 1949, 1887), which described a synthesis of 6-amino-4-hydroxy-2-naphthoic acid ("carboxy γ-acid"), the reasons for undertaking this work were given, and as J-acid (7-amino-4-naphthol-2-sulphonic acid) is one of the most important dyestuffs intermediates of its class it was desirable to synthesise its carboxy-analogue.

Since toluene-*p*-sulphon-2-naphthalide can be nitrated to give the 1 : 6-dinitro-derivative (Morgan and Micklethwait, *J.*, 1912, **101**, 148), it was hoped that 3-toluene-*p*-sulphonamido-2-naphthoic acid (I) would similarly give a dinitro-derivative (II) which could be converted into "carboxy J-acid" by the following route :

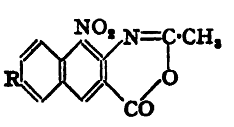


(Tos = p-C_6H_4·SO_2)

3-Amino-2-naphthoic acid reacted with toluene-*p*-sulphonyl chloride to give (I). This was nitrated in glacial acetic acid at 55° to give the 4-nitro-derivative, which on hydrolysis in concentrated sulphuric acid gave 4-nitro-3-amino-2-naphthoic acid, previously prepared by Cross and Drew (*J.*, 1949, 1532) by the nitration of 3-acetamido-2-naphthoic acid. 4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid on further nitration in acetic acid gave a small yield of 4 : 7-dinitro-3-toluene-*p*-sulphonamido-2-naphthoic acid (II), which after hydrolysis to 4 : 7-dinitro-3-amino-2-naphthoic acid was deaminated to give 4 : 7-dinitro-2-naphthoic acid (III). This was decarboxylated to 1 : 6-dinitronaphthalene thus orientating the nitro-groups.

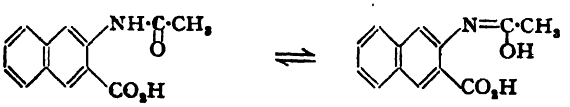
As the yield of (II) was too low to permit a continuation of this synthesis of (IV) the nitration of 4-nitro-3-acetamido-2-naphthoic acid was investigated, but all attempts to obtain a dinitro-compound failed, the mononitro-derivative being recovered unchanged.

A sample of 4 : 7-dinitro-3-acetamido-2-naphthoic acid was prepared by acetylating 4 : 7-dinitro-3-amino-2-naphthoic acid with acetic anhydride and concentrated sulphuric acid. The use of acetic anhydride alone gave the anhydro-derivative (V) which was converted into the acetyl compound by hydrolysis with water.



(V; R = NO_2)
(VI; R = H)

4-Nitro-3-amino-2-naphthoic acid reacted similarly with acetic anhydride to give (VI), whilst the addition of concentrated sulphuric acid gave an inseparable mixture of the acetyl compound and the anhydro-derivative. Hydrolysis of this mixture with water gave 4-nitro-3-acetamido-2-naphthoic acid. 3-Amino-2-naphthoic acid, under similar conditions, gave 3-acetamido-2-naphthoic acid. From these results it is obvious that the nitro-group favours ring closure, by dehydration, of the acetyl compound when acetic anhydride is used. Addition of concentrated sulphuric acid partially prevents this anhydro-formation in the 4-nitro-derivative, and completely prevents it in the 4 : 7-dinitro-derivative.



According to Baker ("Tautomerism," 1934, p. 136) the amide grouping can exist in the tautomeric forms shown above. From the evidence obtained, it seems probable that 3-acetamido-2-naphthoic acid, in the presence of acetic anhydride, normally exists in the keto-form, but the presence of the 4-nitro-group favours the formation of the enol by withdrawing electrons from the side chain, the anhydro-compound being then formed by simple dehydration of the two hydroxyl groups. Addition of concentrated sulphuric acid represses the formation of the *aci*-nitro-form so that the amide remains in the keto-form and hence ring closure does not occur.

Since a route to "carboxy J-acid" using 4 : 7-dinitro-2-naphthoic acid (III) was impossible, practically, owing to the low yield at the second nitration stage, the bromination of 4-nitro-3-acetamido-2-naphthoic acid was investigated. The latter reacted with bromine in boiling glacial acetic acid to give 7-bromo-4-nitro-3-acetamido-2-naphthoic acid (VII), the orientation of which is discussed later.

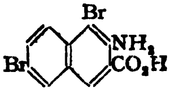
It was found that the yield of (VII) fell if the reaction mixture was heated under reflux after the addition of the bromine:

Time of heating under reflux after addition of bromine, hours	0	1	2½
Yield of (VII), %	63·5	53·7	45·5

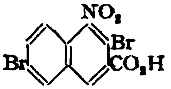
As the only other isolatable product of the reaction was 4-nitro-3-amino-2-naphthoic acid it would appear that (VII) was being reduced by the hydrogen bromide formed in the initial bromination reaction. Fries and Schimmelschmidt (*Annalen*, 1930, **484**, 245) found that the bromination of 2-naphthol is reversible in that 1-bromo- and 1 : 6-dibromo-2-naphthol on treatment with hydrogen bromide in acetic acid afforded 2-naphthol.

Attempts to convert 7-bromo-4-nitro-3-acetamido-2-naphthoic acid (VII) by hydrolysis and deamination into 7-bromo-4-nitro-2-naphthoic acid failed as no method could be found for removing the acetyl group without replacing either the nitro- or the bromo-group, the former by alkaline reagents and the latter by acids.

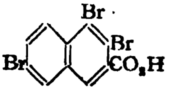
The acetamido-naphthoic acid (VII) reacted with aqueous sodium carbonate to give a compound of unknown structure containing bromine, and with diethylamine to give 7-bromo-3-amino-4-diethylamino-2-naphthoic acid. With ethanol and hydrochloric acid (VII) gave 4-nitro-3-amino-7-ethoxy-2-naphthoic acid and 4-nitro-3-amino-2-naphthoic acid. The formation of the latter compound is unusual and cannot readily be explained. Although (VII) had been reduced to 4-nitro-3-amino-2-naphthoic acid by the action of hydrogen bromide in acetic acid it was thought that aqueous hydrobromic acid would act solely as a deacetylating reagent. The use of 48% hydrobromic acid gave a mixture of 4 : 7-dibromo-3-amino-2-naphthoic acid (VIII) and 3 : 7-dibromo-4-nitro-2-naphthoic acid (IX).



(VIII.)



(IX.)



(X.)

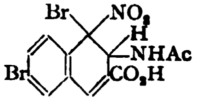
Prager (*Ber.*, 1885, **18**, 2164) found that 4-bromo-2-nitro-1-naphthylamine was converted by hydrobromic acid under pressure into 1 : 2 : 4-tribromonaphthalene. Presumably the milder conditions employed here prevented complete replacement of all the groups by bromine.

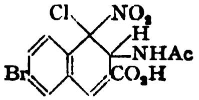
4 : 7-Dibromo-3-amino-2-naphthoic acid (VIII) was converted into 3 : 4 : 7-tribromo-2-naphthoic acid (X) by the Sandmeyer reaction. Attempts to decarboxylate this compound, for orientation purposes, by heating the acid with quinoline and copper powder or by direct distillation, failed, the acid being recovered unchanged. The acid (X) was therefore converted into the amide which would not undergo the Hofmann reaction in aqueous media; but in methanol (cf. Windaus, *Ber.*, 1924, **57**, 1731) 3 : 4 : 7-tribromo-2-naphthylamine was formed, and this was deaminated to give 1 : 2 : 6-tribromonaphthalene.

7-Bromo-4-nitro-3-acetamido-2-naphthoic acid (VII) reacted with 20% hydrobromic acid to give an addition compound which has been formulated as 4 : 7-dibromo-4-nitro-3-acetamido-

3 : 4-dihydro-2-naphthoic acid (XI). This compound reacted with 48% hydrobromic acid to give 3 : 7-dibromo-4-nitro-2-naphthoic acid (IX) and with 2N-sodium carbonate solution to give 4-nitro-3-hydroxy-2-naphthoic acid. (VII) reacted with constant-boiling hydrochloric acid to give 4-chloro-7-bromo-4-nitro-3-acetamido-3 : 4-dihydro-2-naphthoic acid (XII) which likewise gave 4-nitro-3-hydroxy-2-naphthoic acid on treatment with sodium carbonate solution.

(XI.)





(XII.)

Although there are no references to the addition of halogens or halogeno-acids to nitronaphthols or nitronaphthylamines, Fries and Schimmelschmidt (*loc. cit.*) found that bromonaphthols gave addition compounds with hydrogen bromide.

With regard to the formation of 4-nitro-3-hydroxy-2-naphthoic acid from (XI) and (XII) by the action of alkali, Armstrong and Rossiter (*Proc. Chem. Soc.*, 1891, 87—89) found that the addition of nitric acid to 1-bromo-2-naphthol gave 1-bromo-1-nitro-2 : 2-dihydroxy-1 : 2-dihydronaphthalene which immediately decomposed to give 1-bromo-1-nitro-2-keto-1 : 2-dihydronaphthalene. This reacted with alkali to give 1-nitro-2-naphthol. 1 : 6-Dibromo-2-naphthol underwent a similar series of reactions but the final product was 6-bromo-1-nitro-2-naphthol. The loss of the 6-bromine atom in our case is therefore unusual. 4-Nitro-3-amino-2-naphthoic acid is probably a precursor of the 4-nitro-3-hydroxy-2-naphthoic acid since Cross and Drew (*loc. cit.*) found that 4-nitro-3-acetamido-2-naphthoic acid was hydrolysed by sodium hydroxide solution to 4-nitro-3-hydroxy-2-naphthoic acid. This reaction has been repeated by using sodium carbonate instead of sodium hydroxide, and a similar result was obtained.

4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid on treatment with bromine (1 mol.) in glacial acetic acid gave 3 : 4 : 7-tribromo-2-naphthoic acid (X), but in an experiment in which 97·5% acetic acid was accidentally used the product consisted of a mixture of unchanged material and 3 : 7-dibromo-4-nitro-2-naphthoic acid (IX). It was found that 1-nitro-2-acetamidonaphthalene on bromination (1 mol.) in glacial acetic acid gave 1 : 2 : 6-tribromonaphthalene (unpublished work). On these grounds 4-nitro-3-acetamido-2-naphthoic acid might have been expected to give 3 : 4 : 7-tribromo-2-naphthoic acid.

Attempts to brominate 4-nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid in chloroform solution failed. In pyridine, however, 3-bromo-1-nitro-2-toluene-*p*-sulphon-naphthalide was formed. Consden and Kenyon (*J.*, 1935, 1591) prepared this substance by brominating 1-nitro-2-toluene-*p*-sulphon-naphthalide in pyridine. The introduction of a bromine atom in the 3-position of a naphthalene nucleus is not unusual, cf. Consden and Kenyon (*loc. cit.*) and Bell (*J.*, 1932, 2734) who likewise prepared 1 : 3-dibromo-2-toluene-*p*-sulphon-naphthalide.

4 : 7-Dibromo-2-naphthoic acid was prepared from 4 : 7-dibromo-3-amino-2-naphthoic acid (VIII) by deamination. Since it has been shown (unpublished work) that 10% sodium hydroxide at 150° will hydrolyse bromine atoms in a naphthalene ring [cf. Oehler (D.R.-P. 77,446)] 4 : 7-dibromo-2-naphthoic acid was expected to yield 4 : 7-dihydroxy-2-naphthoic acid which on treatment with ammonia and sodium bisulphite would probably yield " carboxy J-acid " (IV) (cf. Bucherer, *J. pr. Chem.*, 1904, **69**, 83). The yield of 4 : 7-dibromo-2-naphthoic acid by this method was too low to permit further work so the halogenation of the acetyl and toluene-*p*-sulphonyl derivatives of 3-amino-2-naphthoic acid itself was investigated.

4-Chloro-3-amino-2-naphthoic acid is the only halogenated 3-amino-2-naphthoic acid described in the literature; it has been prepared from 1-chloro-2 : 3-naphthisatin (F.P. 575, 314; *Chem. Zentr.*, 1925, I, 1021). 2-Acet- and 2-toluene-*p*-sulphon-naphthalide both give 1 : 6-dibromo-derivatives on bromination in acetic acid or chloroform (Bell, *loc. cit.*; Franzen and Stauble, *J. pr. Chem.*, 1921, **107**, 58). 3-Toluene-*p*-sulphonamido-2-naphthoic acid was brominated in pyridine to give 4-bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid, which was hydrolysed and decarboxylated to give 1-bromo-2-naphthylamine. Attempts to brominate 4-bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid in glacial acetic acid gave a tribromo-compound, presumably 4 : 5 : 7-tribromo-3-amino-2-naphthoic acid, which was also formed from 3-toluene-*p*-sulphonamido-2-naphthoic acid and bromine (1 mol.) in acetic acid. 3-Acetamido-2-naphthoic acid failed to brominate in glacial acetic acid and was only partly brominated in pyridine, giving an inseparable mixture.

Attempts to nitrate 4-bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid, to give the 7-nitro-compound failed, even in the presence of a boron trifluoride catalyst.

EXPERIMENTAL.

(Analyses are by Mr. E. S. Morton. M. p.s are uncorrected.)

Nitro-derivatives of 3-*Amino*-2-*naphthoic acid.*

3-*Toluene*-p-*sulphonamido*-2-*naphthoic Acid.*—A solution of 3-amino-2-naphthoic acid (250 g.) in water (2·5 l.) and 10N-sodium hydroxide (135 c.c.) was filtered, the filtrate heated to 75° and toluene-*p*-sulphonyl chloride (275 g.) gradually added while the mixture was kept slightly alkaline to litmus by the addition of sodium carbonate. The boiling mixture was made alkaline to brilliant-yellow paper and filtered. The hot filtrate was added to water (300 c.c.) and concentrated hydrochloric acid (300 c.c.), and the solid was collected, washed with water, and dried. Crystallisation of this first from glacial acetic acid (1360 c.c.) then from methanol gave 3-*toluene*-p-*sulphonamido*-2-*naphthoic acid* as creamy white prisms (238 g.), m. p. 224° (Found: C, 63·5; H, 4·35; N, 4·0. $C_{18}H_{15}O_4NS$ requires C, 63·4; H, 4·4; N, 4·1%).

4-*Nitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic Acid.*—The sulphonamido-compound (51 g.) in glacial acetic acid (150 c.c.) was heated to 100°, then cooled to 54° with stirring. Sodium nitrite (0·1 g.) was added, followed by nitric acid (12·6 c.c.; *d* 1·4), the temperature being held at 54—57°. The solution was cooled to 10°, and the product was collected, washed with glacial acetic acid and carbon tetrachloride, and dried. Crystallisation of the solid from glacial acetic acid gave pale yellow prisms (39 g.), m. p. 188° (decomp.), of 4-*nitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic acid* (Found: C, 56·1; H, 3·8; N, 7·4. $C_{18}H_{14}O_6N_2S$ requires C, 56·0; H, 3·65; N, 7·25%).

4-*Nitro*-3-*amino*-2-*naphthoic Acid.*—The foregoing toluene-*p*-sulphonyl compound (30 g.) was dissolved in concentrated sulphuric acid (60 c.c.) at 30—40°, the solution poured on to ice, and the solid collected, washed with water, and dried. Crystallisation of the product from methanol gave orange needles (15 g.), m. p. 243—244° [Cross and Drew, *loc. cit.*, gave m. p. 240° (decomp.)] (Found: C, 57·3; H, 3·8; N, 12·1. Calc. for $C_{11}H_8O_4N_2$: C, 56·9; H, 3·45; N, 12·1%).

4 : 7-*Dinitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic Acid.*—4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid (19·3 g.) was boiled with glacial acetic acid (50 c.c.), cooled to 60°, and nitric acid (3·5 c.c.; *d* 1·5) added. The mixture was heated to 100° whereupon a reaction began. After 5 minutes the solution was cooled to 10°, and the solid collected, washed with glacial acetic acid then with carbon tetrachloride, and dried. Crystallisation of the solid from ethyl acetate gave pale yellow needles (3·7 g.), m. p. 177° (explosion), of 4 : 7-*dinitro*-3-*toluene*-p-*sulphonamido*-2-*naphthoic acid* (Found: C, 49·25; H, 2·15. $C_{18}H_{13}O_8N_3S$ requires C, 50·1; H, 3·0%).

4 : 7-*Dinitro*-3-*amino*-2-*naphthoic Acid.*—The toluene-*p*-sulphonyl derivative (3·6 g.) was dissolved in concentrated sulphuric acid (8 c.c.) at 35—40°, the solution poured on to ice, and the solid collected, washed with water, and dried. Crystallisation of the product from ethyl acetate gave orange micro-crystals (2·1 g.), m. p. 302°, of the *dinitroaminonaphthoic acid* (Found: C, 47·4; H, 2·6; N, 14·7. $C_{11}H_7O_6N_3$ requires C, 47·6; H, 2·55; N, 15·2%).

4 : 7-*Dinitro*-2-*naphthoic Acid.*—The 3-amino-compound (1 g.) was deaminated by the method of Hodgson and Walker (*J.*, 1933, 1620). Crystallisation of the *dinitronaphthoic acid* from glacial acetic acid gave yellowish brown micro-crystals (0·4 g.), m. p. 230—231° (Found: C, 50·7; H, 3·1; N, 10·3. $C_{11}H_6O_6N_2$ requires C, 50·4; H, 2·3; N, 10·7%).

Decarboxylation of 4 : 7-*Dinitro*-2-*naphthoic Acid.*—The dinitro-compound (0·2 g.) on being heated with copper bronze (0·2 g.) and quinoline (5 c.c.) for 10 minutes gave 1 : 6-dinitronaphthalene as pale yellow needles (from methanol), m. p. 163—164°, not depressed by admixture with an authentic sample.

3-*Acetamido*-2-*naphthoic Acid.*—3-Amino-2-naphthoic acid (100 g.), dissolved in water (800 c.c.) and 10N-sodium hydroxide (50 c.c.), was treated at 40° with acetic anhydride (80 c.c.). After the solution had been stirred for 1 hour excess of hydrochloric acid was added, and the solid was collected, washed with water, and dried. It was purified by treatment with boiling methanol, and dried. The product (90 g.) had m. p. 234—235°. An analytical specimen crystallised from ethanol in pale yellow needles, m. p. 237—238° (lit. gives m. p. 238°) (Found: C, 67·8; H, 4·95; N, 6·55. Calc. for $C_{13}H_{11}O_3N$: C, 68·1; H, 4·8; N, 6·1%).

3-Amino-2-naphthoic acid (2 g.) was heated under reflux with acetic anhydride (4 c.c.) for 2 hours, the solution poured into water, and the product crystallised from ethanol to give 3-acetamido-2-naphthoic acid (1·7 g.), m. p. 237—238°.

4-*Nitro*-3-*acetamido*-2-*naphthoic Acid.*—The following method was found to be preferable to that reported by Cross and Drew (*loc. cit.*). 3-Acetamido-2-naphthoic acid (20 g.) and glacial acetic acid (140 c.c.) were heated to 80° and treated with sodium nitrite (0·1 g.) and nitric acid (8 c.c.; *d* 1·42). The temperature was cautiously raised to 95°, and as soon as a clear solution was obtained the reaction mixture was cooled. After 12 hours the solid (18 g.) was collected, washed with carbon tetrachloride, and dried. Crystallisation of the solid from glacial acetic acid gave rosettes of pale yellow needles, m. p. 199—200° (Found: C, 57·1; H, 3·45; N, 10·0. Calc. for $C_{13}H_{10}O_5N_2$: C, 56·9; H, 3·65; N, 10·2%).

Hydrolysis of the *acetyl* compound (4·4 g.) with a boiling mixture of ethanol (44 c.c.) and concentrated hydrochloric acid (22 c.c.) for 1½ hours gave 4-nitro-3-amino-2-naphthoic acid (2·2 g.), m. p. 243—244°.

Acetylation of 4-*Nitro*-3-*amino*-2-*naphthoic Acid.*—4-Nitro-3-amino-2-naphthoic acid (3 g.) and acetic anhydride (15 c.c.) were heated under reflux for 6 hours and cooled, and the crystalline solid collected. Crystallisation of this from glacial acetic acid gave yellow needles (2·7 g.) of *anhydro*-4-*nitro*-3-*acetamido*-2-*naphthoic acid*, m. p. 234—235°, insoluble in cold, dilute sodium carbonate solution (Found: C, 60·4; H, 3·1; N, 10·9. $C_{13}H_8O_4N_2$ requires C, 60·95; H, 3·1; N, 10·9%).

This compound (0·5 g.) was heated under reflux with water (40 c.c.) for 30 hours, sodium carbonate solution added, the mixture filtered, and the filtrate acidified. The product was collected and crystallised from glacial acetic acid to give pale yellow needles (0·4 g.) of 4-*nitro*-3-*acetamido*-2-*naphthoic acid*, m. p. 199—200°.

Acetylation of 4 : 7-*Dinitro*-3-*amino*-2-*naphthoic Acid.*—4 : 7-Dinitro-3-amino-2-naphthoic acid (1 g.) and acetic anhydride (5 c.c.) were heated under reflux for 1 hour, water was added, and the solid was collected and crystallised from glacial acetic acid to give creamy white needles (0·8 g.) of *anhydro-*4 : 7-*dinitro-*3-*acetamido-*2-*naphthoic acid*, m. p. 202—203°, insoluble in cold, dilute sodium carbonate solution (Found : C, 51·4; H, 2·65; N, 13·7. $C_{13}H_7O_6N_3$ requires C, 51·8; H, 2·3; N, 14·0%).

This compound (0·1 g.) and water (40 c.c.) were heated under reflux for 18 hours, sodium carbonate was added, the mixture was filtered, and the filtrate was acidified. Crystallisation from glacial acetic acid of the solid so obtained gave yellow micro-crystals of 4 : 7-*dinitro-*3-*acetamido-*2-*naphthoic acid*, m. p. 262° (Found : C, 48·6; H, 3·25; N, 12·6. $C_{13}H_9O_7N_3$ requires C, 48·9; H, 2·8; N, 13·1%).

4 : 7-Dinitro-3-amino-2-naphthoic acid (0·5 g.), treated with acetic anhydride (3 c.c.) and concentrated sulphuric acid (0·2 c.c.), gave the acetyl derivative, m. p. 261—262°.

Halogenated Nitro-derivatives of 3-*Amino-*2-*naphthoic Acid*

7-*Bromo-*4-*nitro-*3-*acetamido-*2-*naphthoic Acid.*—(*a*) Bromine (18·6 c.c.) in glacial acetic acid (50 c.c.) was added to a boiling solution of 4-nitro-3-acetamido-2-naphthoic acid (100 g.) in glacial acetic acid (1220 c.c.). A vigorous reaction took place, and after 15 minutes the solution was cooled in ice and the solid collected. Crystallisation of this from glacial acetic acid gave pale yellow needles (82 g.; 63·5%), m. p. 228—229° (Found : C, 43·7; H, 2·75; N, 7·45; Br, 23·5. $C_{13}H_9O_5N_2Br$ requires C, 44·1; H, 2·55; N, 7·9; Br, 22·5%).

(*b*) The same quantities were used but the mixture was heated under reflux for 1 hour after the addition of the bromine. The yield was 53·7%.

(*c*) The time of heating under reflux was increased to 2½ hours, and the yield obtained was 45·5%.

The acetic acid mother liquors were diluted with water, and the resulting sticky solid was crystallised from methanol giving 4-nitro-3-amino-2-naphthoic acid (26·5%). The methanol mother liquors were concentrated, and the residue heated under reflux with ethanol (200 c.c.) and concentrated hydrochloric acid (100 c.c.) for 2 hours. Water was added, and the solid was collected and crystallised from glacial acetic acid to give 4-nitro-3-amino-2-naphthoic acid (16%).

Bromination of 4-*Nitro-*3-*toluene-*p-*sulphonamido-*2-*naphthoic Acid in Glacial Acetic Acid.*—4-Nitro-3-toluene-*p*-sulphonamido-2-naphthoic acid (38·6 g.) was dissolved in boiling glacial acetic acid (250 c.c.) and bromine (5·4 c.c.; 1 mol.) added. After the solution had been heated under reflux for 6 hours it was cooled and the solid (12 g.) collected. Crystallisation of this from glacial acetic acid gave pale cream needles of 3 : 4 : 7-*tribromo-*2-*naphthoic acid*, m. p. 244—245° (Found : C, 33·0; H, 1·4; Br, 58·7. $C_{11}H_5O_2Br_3$ requires C, 32·3; H, 1·2; Br, 58·6%).

Orientation of 3 : 4 : 7-*Tribromo-*2-*naphthoic Acid.*—(a) 3 : 4 : 7-*Tribromo-*2-*naphthoamide*. The acid (14 g.) in benzene (40 c.c.) was heated under reflux with thionyl chloride (4 c.c.) for 7 hours, the solution cooled, and excess of ammonium carbonate added. After 2 hours the benzene was removed by steam, and the solid was collected and washed with hot water. Crystallisation of this from β-ethoxyethanol gave white micro-crystals of the *amide* (10 g.), m. p. >280° (Found : C, 32·2; H, 1·75; N, 3·7. $C_{11}H_6ONBr_3$ requires C, 32·3; H, 1·5; N, 3·4%).

(b) 3 : 4 : 7-*Tribromo-*2-*naphthylamine*. The amide (9·3 g.) was suspended in methanol (100 c.c.) and sodium hypochlorite solution (17 c.c.; 15%) added, the temperature rising to 45°. After 15 minutes, 10N-sodium hydroxide (25 c.c.) and methanol (40 c.c.) were added. The methanol was removed by distillation and the residue extracted with water. Crystallisation of the *amine* from ethanol gave white needles (4·2 g.), m. p. 157—159° (Found : C, 31·4; H, 1·65; N, 3·65. $C_{10}H_6NBr_3$ requires C, 31·6; H, 1·6; N, 3·7%).

The *acetyl* derivative, prepared from the amine and acetic anhydride, crystallised from acetic acid in white needles, m. p. 205—206° (Found : C, 34·2; H, 1·85. $C_{12}H_8ONBr_3$ requires C, 34·1; H, 1·9%).

(c) 3 : 4 : 7-*Tribromonaphthalene*. The amine (1·2 g.) was deaminated by the method used for 4 : 7-dinitro-3-amino-2-naphthoic acid. Crystallisation from acetic acid gave white needles of 3 : 4 : 7-tribromonaphthalene, m. p. 113—114° not depressed by admixture with an authentic sample.

Bromination of 4-*Nitro-*3-*toluene-*p-*sulphonamido-*2-*naphthoic Acid in* 97·5% *Acetic Acid.*—The compound (19·3 g.) was dissolved in boiling acetic acid (125 c.c.), and bromine (2·7 c.c.) added. After the solution had been heated under reflux for 6 hours, and cooled, water (450 c.c.) was added. The solid obtained (11 g.) was dissolved in ethanol and chromatographed on alumina. The upper band was separated, extracted with sodium carbonate, the extract filtered, and the filtrate acidified. The solid (4 g.), m. p. 186—188°, obtained was shown to be unchanged. The lower band was similarly separated. Crystallisation from acetic acid of the solid obtained gave 3 : 7-*dibromo-*4-*nitro-*2-*naphthoic acid* (3·2 g.), m. p. and mixed m. p. (see below) 234—236°.

Bromination of 1-*Nitro-*3-*toluene-*p-*sulphonamido-*2-*naphthoic Acid in Pyridine.*—A solution of the compound (7·7 g.) in pyridine (30 c.c.) was cooled to 5° and treated with a cold solution of bromine (1·2 c.c.) in pyridine (10 c.c.). After 15 minutes the solution was run into a mixture of ice and concentrated hydrochloric acid, and the solid was collected and washed with water. Crystallisation of it from dioxan gave orange micro-crystals (3·5 g.) of 3-bromo-1-nitro-2-toluene-*p*-sulphon-naphthalide, m. p. 229—231° (Consden and Kenyon, *loc. cit.*, give m. p. 237°) (Found : C, 48·5; H, 2·85; N, 6·4; Br, 18·4. Calc. for $C_{17}H_{13}O_4N_2BrS$: C, 48·5; H, 3·1; N, 6·65; Br, 19·0%).

The amine, prepared from the toluene-*p*-sulphonyl derivative by hydrolysis with concentrated sulphuric acid, crystallised from ethanol in red needles, m. p. 100—101° (Consden and Kenyon, *loc. cit.*, give m. p. 105°) (Found : C, 45·0; H, 2·7; N, 10·4. Calc. for $C_{10}H_7O_2N_2Br$: C, 45·0; H, 2·6; N, 10·5%).

Reactions of 7-*Bromo-*4-*nitro-*3-*acetamido-*2-*naphthoic Acid.*—(a) *With sodium carbonate solution.* The compound (2 g.) was heated under reflux with 2N-sodium carbonate solution (30 c.c.) for 20 hours, cooled, and acidified with hydrochloric acid. The solid was collected and crystallised from glacial acetic acid to give yellow micro-crystals (1 g.), m. p. >300° (Found : C, 50·95, 51·2; H, 2·95, 3·0; N, 7·95, 7·65; Br, 21·3%). No structural formula can be ascribed to these figures which agree best with $C_{15}H_{11}O_4N_2Br$ (C, 49·6; H, 3·0; N, 7·7; Br, 22·0%) or $C_{16}H_{11}O_4N_2Br$ (C, 51·0; H, 2·95; N, 7·5; Br, 21·4%).

(b) *With diethylamine.* The compound (3 g.) and diethylamine (35 c.c.) were heated under reflux for 24 hours, the excess of diethylamine removed by distillation, and excess of 2N-sodium hydroxide added. After being heated on a steam-bath for 1 hour the solution was filtered and acidified (litmus) with acetic acid; the solid was collected and crystallised from glacial acetic acid to give *7-bromo-3-amino-4-diethylamino-2-naphthoic acid* as a pale brown powder (2 g.), m. p. >310° (Found: C, 53·8, 53·6; H, 4·65, 4·7; N, 8·3, 8·0; Br, 23·1. $C_{15}H_{17}O_2N_2Br$ requires C, 53·4; H, 5·0; N, 8·3; Br, 23·7%).

(c) *With 48% hydrobromic acid.* The compound (10 g.) and hydrobromic acid (90 c.c.; 48%) were heated under reflux for 24 hours and poured into water (500 c.c.). The solid which was collected was fractionally crystallised from glacial acetic acid; it gave a sparingly soluble product, 4 : *7-dibromo-3-amino-2-naphthoic acid* (bright yellow needles) (2·0 g.), m. p. 256—257° (Found: C, 37·8; H, 1·95; N, 3·8; Br, 46·7. $C_{11}H_7O_2NBr_2$ requires C, 38·3; H, 2·0; N, 4·1; Br, 46·4%), and an easily soluble portion which crystallised from ethanol to give orange needles (1·5 g.) of 3 : *7-dibromo-4-nitro-2-naphthoic acid*, m. p. 236—238° (Found: C, 35·4; H, 1·6; N, 3·45; Br, 43·0. $C_{11}H_5O_4NBr_2$ requires C, 35·2; H, 1·3; N, 3·7; Br, 42·7%).

4 : 7-Dibromo-3-amino-2-naphthoic acid (1·0 g.) in glacial acetic acid (8·0 c.c.) was added to a solution of sodium nitrite (0·35 g.) in concentrated sulphuric acid (3·5 c.c.) at 20—25°. The diazo-compound was then added to cuprous bromide (1 g.) in hydrobromic acid (10 c.c.; 48%), the mixture was stirred for 1 hour, water added, and the solid collected. Crystallisation of this ffom acetic acid gave 3 : 4 : 7-tribromo-2-naphthoic acid, m. p. and mixed m. p. 244—245°.

By a similar reaction 4 : 7-dibromo-3-amino-2-naphthoic acid (0·6 g.) gave 3-*chloro*-4 : *7-dibromo-2-naphthoic acid* as pale yellow needles (0·3 g.), m. p. 234—236°, from acetic acid (Found: C, 36·0; H, 1·5. $C_{11}H_5O_2ClBr_2$ requires C, 36·2; H, 1·4%).

4 : 7-Dibromo-3-amino-2-naphthoic acid (1 g.) was deaminated by Hodgson and Walker's method (*loc. cit.*) giving 4 : *7-dibromo-2-naphthoic acid* (0·6 g.), m. p. 258—259° (Found: C, 39·9; H, 2·15. $C_{11}H_6O_2Br_2$ requires C, 40·0; H, 1·8%).

(d) *With dilute hydrobromic acid.* The compound (7 g.) was heated under reflux with hydrobromic acid (19 c.c.; 48%) and water (38 c.c.) for 24 hours, water (150 c.c.) was added, and the solid (6·5 g.) was collected. Crystallisation of this from glacial acetic acid gave pale yellow micro-needles (3·8 g.) of 4 : *7-dibromo-4-nitro-3-acetamido*-3 : *4-dihydro-2-naphthoic acid*, m. p. 240—242° (Found: C, 35·6; H, 2·5; N, 6·2; Br, 36·3. $C_{13}H_{10}O_5N_2Br_2$ requires C, 35·9; H, 2·3; N, 6·45; Br, 36·8%).

This compound (1·3 g.) was heated under reflux with hydrobromic acid (25 c.c.; 48%) for 20 hours and diluted with water. The solid (1 g.) was crystallised from acetic acid and gave orange needles, m. p. 234—236°, of 3 : 7-dibromo-4-nitro-2-naphthoic acid.

The compound (0·5 g.) was heated under reflux with 2N-sodium carbonate (20 c.c.) for 6 hours, hydrochloric acid was added, and the solid was collected; it crystallised from acetic acid in yellow needles (0·2 g.) of *4-nitro-3-hydroxy-2-naphthoic acid*, m. p. 234—236° not depressed by admixture with an authentic sample (Found: C, 56·4; H, 3·2; N, 5·9. Calc. for $C_{11}H_7O_5N$: C, 56·5; H, 3·0; N, 6·0%).

(e) *With hydrochloric acid.* The compound (7 g.), concentrated hydrochloric acid (140 c.c.), and water (70 c.c.) were heated under reflux for 24 hours, water (150 c.c.) was added, and the solid was collected, boiled with ethanol (100 c.c.), and filtered off. *4-Chloro-7-bromo-4-nitro-3-acetamido*-3 : *4-dihydro-2-naphthoic acid* (3·5 g.) crystallised from acetic acid as creamy white needles, m. p. 239—240° (Found: C, 39·7, 40·0; H, 2·25, 2·4; N, 6·95, 7·3; Cl + Br, 28·6. $C_{13}H_{10}O_5N_2ClBr$ requires C, 40·05; H, 2·6; N, 7·2; Cl + Br, 29·7%).

This compound on hydrolysis with 2N-sodium carbonate gave 4-nitro-3-hydroxy-2-naphthoic acid.

(f) *With hydrochloric acid and ethanol.* The compound (10 g.), ethanol (200 c.c.), and concentrated hydrochloric acid (75 c.c.) were heated under reflux for 48 hours and water was added. The resultant solid was dissolved in methanol and chromatographed on alumina. A band, which remained at the top of the column, was extracted with sodium carbonate, acidified, and crystallised from ethanol giving 4-nitro-3-amino-2-naphthoic acid (2·0 g.), m. p. and mixed m. p. 238—240°. The remaining material was isolated by concentration of the eluate, and the solid crystallised from methanol to give orange needles (1 g.), m. p. 103—104°, of *4-nitro-3-amino-7-ethoxy-2-naphthoic acid* (Found: C, 56·9; H, 4·1; N, 10·65. $C_{13}H_{12}O_5N_2$ requires C, 56·5; H, 4·35; N, 10·2%).

Bromo-derivatives of 3-Amino-2-naphthoic Acid.

*4-Bromo-3-toluene-*p*-sulphonamido-2-naphthoic Acid.*—3-Toluene-*p*-sulphonamido-2-naphthoic acid (8·5 g.) was dissolved in pyridine (40 c.c.), and an ice-cold solution of bromine (1·3 c.c.) in pyridine (10 c.c.) added. Next morning the solution was poured into excess of hydrochloric acid, and the solid was collected and crystallised from glacial acetic acid to give the 4-*bromo*-compound as pale yellow needles, m. p. 197—198° (5 g.) (Found: C, 51·7; H, 3·55; N, 3·75. $C_{18}H_{14}O_4NBrS$ requires C, 51·4; H, 3·3; N, 3·4%).

4-Bromo-3-amino-2-naphthoic Acid.—The toluene-*p*-sulphonyl compound (5 g.) was dissolved in concentrated sulphuric acid (10 c.c.) at 35—40°, the solution poured on to ice, and the solid collected. Crystallisation of this from glacial acetic acid gave bright yellow needles (2 g.), m. p. 220—222° (Found: C, 49·1; H, 3·05; N, 5·7. $C_{11}H_8O_2NBr$ requires C, 49·6; H, 3·0; N, 5·25%).

On decarboxylation in quinoline in the presence of copper bronze, 1-bromo-2-naphthylamine, m. p. and mixed m. p. with an authetic sample 61—63°, was obtained.

4 : 5 : 7(?)-*Tribromo-3-amino-2-naphthoic Acid.*—(*a*) 3-Toluene-*p*-sulphonamido-2-naphthoic acid (10·2 g.) in boiling glacial acetic acid (100 c.c.) was treated with bromine (4·6 c.c.; 3 mols.). After being heated under reflux for 1 hour the solution was cooled and the solid (8 g.) collected. Crystallised from glacial acetic acid it gave yellow micro-crystals, m. p. 254°, of a *tribromo*-compound (Found: C, 30·9; H, 1·9; N, 3·3; Br, 56·0. $C_{11}H_6O_2NBr_3$ requires C, 31·2; H, 1·4; N, 3·3; Br, 56·6%).

(*b*) 4-Bromo-3-toluene-*p*-sulphonamido-2-naphthoic acid (4·1 g.) in boiling glacial acetic acid (20 c.c.) was treated with bromine (0·5 c.c., 1 mol.). After being heated under reflux for 30 minutes the solution was cooled and the solid collected. Crystallisation of this from acetic acid gave 2 g. of a solid, m. p. 253—254°, identical with the previous compound.

RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
BLACKLEY, MANCHESTER, 9.

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199. *Amine-N-glycosides. Part I. Arylamine-N-glucosides.*

By John Honeyman and A. R. Tatchell.

Aniline and glucose react under various conditions to give the same aniline-*N*-glucoside, which mutarotates in several solvents. Acetylation of aniline-*N*-glucoside gives a mixture of α- and β-aniline-*N*-glucopyranoside tetra-acetates which can be deacetylated to the original aniline-*N*-glucoside.

p-Toluidine-*N*-glucoside is obtained in a pure crystalline form which has been acetylated to β-*p*-toluidine-*N*-glucopyranoside tetra-acetate.

The pyranose ring structure of these amine-*N*-glucosides is probable, but not certain.

The reaction products obtained when sugars react with amines have been known for many years, but although much work has been carried out to determine their structure there is still no clear picture of their nature. The early workers (Schiff, *Annalen*, 1870, **154**, 30; Sorokin, *Ber.*, 1886, **19**, 513) prepared compounds whose structures were considered to be of the Schiff's base type (Schiff and Straus, *Ber.*, 1894, **27**, 1287) or of the cyclic glycosidic type (Marchlewski, *J. prakt. Chem.*, 1894, [ii], **50**, 95). The methylation studies of Irvine and his co-workers from 1908 to 1911 (*e.g.*, Irvine and Hynd, *J.*, 1911, **99**, 161) furnished strong evidence of the cyclic nature of these compounds. Their isolation of tetramethyl aniline-*N*-glucopyranoside was held to be evidence for considering the mutarotating aniline-*N*-glucoside to be α- and β-aniline-*N*-glucopyranosides. Since then, certain arylamine-*N*-pentosides have been prepared which have been assigned the furanose structure solely on the basis of their reaction with triphenylmethyl chloride. In particular, certain arylamine-*N*-pentosides have thus been held to be furanosides (Kuhn and Ströbele, *Ber.*, 1937, **70**, 773) although later workers claim to have shown that at least one of these is actually a pyranoside (mentioned by Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 855, but details not yet published). Similarly, xylidine-*N*-riboside prepared in boiling alcohol is considered to be a furanoside (Kuhn and Birkofer, *Ber.*, 1938, **71**, 621), whereas the xylidine-*N*-riboside prepared in alcohol at room temperature is thought to be a pyranoside (Berger and Lee, *J. Org. Chem.*, 1946, **11**, 75). Under similar conditions aniline reacts with ribose to give two aniline-*N*-ribosides (Berger and Lee, *loc. cit.*); these were cyclic because acetylation of each led to a triacetate; although the triacetates were glasses, no characteristic physical data were given, and they had acetyl contents somewhat lower than the theoretical. Berger and Lee held that they were distinct compounds. Removal of the aniline residue from each gave two amorphous ribose triacetates (Berger, Solmssen, Leonard, Wenis, and Lee, *J. Org. Chem.*, 1946, **11**, 91). These workers considered them to be ribose 2 : 3 : 4-triacetate (from aniline-*N*-ribopyranoside) and ribose 2 : 3 : 5-triacetate (from aniline-*N*-ribofuranoside). Examination of the data of these workers shows that one of the compounds, with acetyl content 40·9% (theoretical, 46·7%), had $[\alpha]^{20}_{D}$ −26·3°, while the other, of acetyl content 41·5%, had $[\alpha]^{20}_{D}$ −24·2°. It is considered, therefore, that there is no evidence that two distinct aniline-*N*-riboside triacetates have been prepared. On the contrary, other workers (Todd *et al.*, *loc. cit.*) have shown that the two aniline-*N*-ribosides are acetylated to the same aniline-*N*-ribopyranoside 2 : 3 : 4-triacetate. Furthermore, Berger and Lee have shown that benzoylation of the two aniline-*N*-ribosides, followed by hydrogenation, gives the same ribitylaniline tribenzoate. The sole remaining chemical evidence for the pyranose and furanose structures assigned to the aniline-*N*-ribosides rests on the reaction of the compounds with triphenylmethyl chloride. This reagent is now known to be unsatisfactory for detecting primary alcohol groups such as would be present in aniline-*N*-ribofuranoside and absent in aniline-*N*-ribopyranoside, for it reacts with secondary as well as with primary alcohol groups (Hockett and Hudson, *J. Amer. Chem. Soc.*, 1931, **53**, 4456; McIlroy, *J.*, 1946, 100). Crystalline triphenylmethyl derivatives of β-methylxylopyranoside, a compound similar in structure to aniline-*N*-ribopyranoside, have been isolated (Jackson, Hockett, and Hudson, *J. Amer. Chem. Soc.*, 1934, **56**, 947).

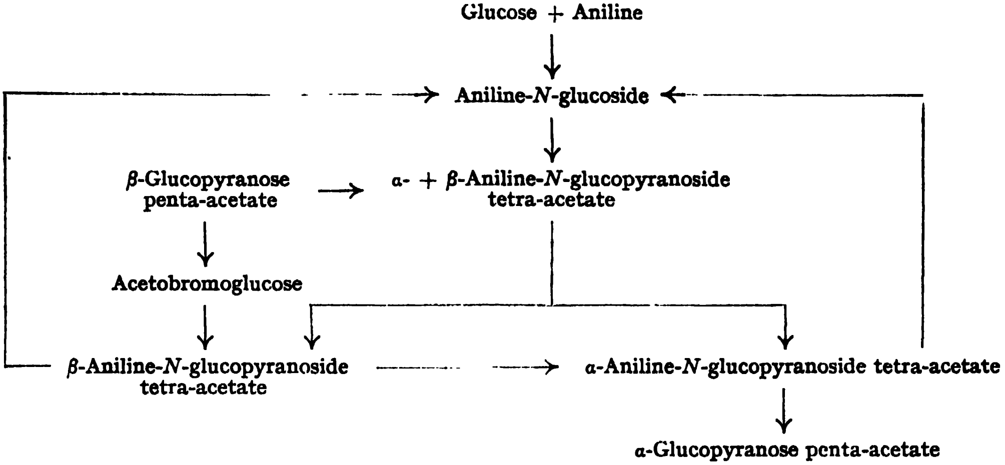
Indeed, the work of Berger and Lee really confirms the unsatisfactory nature of this reagent. From the compound they consider to be aniline-*N*-ribofuranoside they isolated a tan-coloured amorphous product giving the elementary analysis of a monotrityl aniline-*N*-riboside combined with 1·75 molecules of water. No attempt was made to show that the trityl residue was attached to $C_{(5)}$. Under similar conditions the aniline-*N*-ribopyranoside gave a tarry product which could not be purified. It is clear that Berger and Lee have not shown that this second isomer reacts less readily with triphenylmethyl chloride. Methylation studies have been unproductive (Berger and Lee, *loc. cit.*), probably because of the instability of the *N*-glycosides to alkali. Oxidation with periodate has also been found to be of no value (Berger and Lee, *loc. cit.*; Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 861). It seems fair to say, therefore, that there has been no chemical evidence presented so far for assigning the furanose structure to one of the aniline-*N*-ribosides. No derivative with this structure has been isolated. Of the physical data the melting points, as Berger and Lee point out, are unreliable. For 3 : 4-xylidine-*N*-ribofuranoside Kuhn and Birkofer (*loc. cit.*) give m. p. 118°, whereas this compound prepared identically was found by Berger and Lee to have m. p. 128—130°. The corresponding pyranoside of these workers has m. p. 110—112°. For aniline-*N*-ribopyranoside Todd and his co-workers give m. p. 119°, whereas Berger and Lee give m. p. 125—127°. For the corresponding furanoside the former workers give m. p. 126—127°, whereas the latter record m. p. 138—140°. In addition, Berger and Lee have found that mixing the two aniline-*N*-ribosides does not, as a rule, lead to a depressed melting point.

It remains to consider the specific rotations, and here lies the sole evidence for the existence of the two ring-isomers of arylamine-*N*-ribosides. The 3 : 4-xylidine-*N*-ribopyranoside has $[\alpha]_D^{24}$ $+171\cdot7° \longrightarrow +56\cdot5°$ (*c*, 0·5 in pyridine), while the corresponding furanoside has $[\alpha]_D^{25}$ $+94\cdot5° \longrightarrow +53\cdot0°$ (*c*, 1 in pyridine). The final values are so close that no conclusion that they represent α- + β-ribopyranosides and α- + β-ribofuranosides, respectively, is tenable. It might as well be that the former compound is, say, pure α-pyranoside mutarotating to an equilibrium mixture of α- + β-pyranoside, whereas the latter is a mixture of α- and β-pyranosides, richer in the β-anomer, mutarotating to the same equilibrium mixture of α- + β-pyranosides. With the aniline-*N*-ribosides the difference in specific rotation is marked and appears to be conclusive. The product of condensation in boiling alcohol, considered by Berger and Lee to be aniline-*N*-ribofuranoside, has $[\alpha]_D^{27}$ $+176\cdot5° \longrightarrow +156\cdot6°$ (*c*, 3 in pyridine) (Berger and Lee; Todd *et al.*), whereas the product of condensation in alcohol at room temperature, considered to be the pyranoside, has $[\alpha]_D^{24}$ $+63\cdot4° \longrightarrow +48\cdot6°$ (*c*, 1 in pyridine) (Berger and Lee; Todd *et al.*), and, since the two compounds mutarotate in the same direction but not to the same final equilibrium value, there appears to be a strong case for believing that two different ring-isomers have been obtained. There is, however, no acceptable evidence for deciding which has the furanose and which the pyranose structure. Thus, Berger and Lee's belief that the pyranose compound was converted into the more stable furanose compound simply by refluxing in alcohol or slowly at room temperature in alcohol, or by drying over phosphoric oxide in a vacuum, requires further investigation. (This investigation has already been begun in our laboratories.)

The case of the aniline-*N*-D-arabinosides must also be mentioned. The product of condensation in alcohol at room temperature, considered by Berger and Lee (*J. Org. Chem.*, 1946, **11**, 84), by analogy with the ribosides, to be aniline-*N*-arabinopyranoside, has m. p. 130°, $[\alpha]_D^{28}$ $+8\cdot9° \longrightarrow -13\cdot2°$ (*c*, 1·9 in methanol, after 48 hours), $[\alpha]_D^{29}$ $+68° \longrightarrow -4\cdot2°$ (*c*, 3 in pyridine, after 48 hours). The product, prepared in boiling alcohol by following the same procedure as an earlier worker [Hanaoka, *J. Biochem.* (*Japan*), 1940, **31**, 95], had m. p. 130°, $[\alpha]_D^{20}$ $+27\cdot4° \longrightarrow -8\cdot0°$ (*c*, 1·6 in methanol, after 24 hours), $[\alpha]_D^{29}$ $+82° \longrightarrow +1\cdot48°$ (*c*, 2 in pyridine, after 24 hours). Hanaoka cites m. p. 130°, $[\alpha]_D^{20}$ $+34° \longrightarrow +2\cdot5°$ (*c*, 1 in methanol). Again the values are too similar for certainty that different ring forms are present: the alternative explanation advanced in the case of the xylidine-*N*-ribosides appears to be equally valid.

It was in the light of the papers discussed above that the present work was started. During the course of this investigation it has been found that glucose reacts with aniline in boiling alcohol (Sorokin, *loc. cit.*), in aqueous alcohol at room temperature, and in boiling water (Weygand, *Ber.*, 1939, **72**, 1663), to give the same aniline-*N*-glucoside, mutarotating in methanol from an initial value of about +10° to a final value of about −52°. Despite many attempts to prepare this compound and to obtain it in a pure stable form it has invariably been obtained as a white solid which is not truly crystalline. It is precipitated from several solvents in a jelly-like form from which the last traces of solvent are difficult to remove, owing, it is considered, to the physical form of the product. When dry it is a hard white powder which, however, is unstable, becoming brown on storage at room temperature, even in a vacuum desiccator. Aniline-*N*-glucoside, like all compounds of this type, is readily hydrolysed by dilute acids. It is also attacked by aqueous alkali, and it therefore reduces Fehling's solution rapidly. No reproducible melting point was obtained for this product. Acetylation was successfully achieved with acetic anhydride in pyridine; under somewhat different conditions a similar mixture of tetra-acetates was obtained. The components of the mixture were shown to have pyranose structure since the removal of the aniline residue, followed by acetylation with acetic anhydride and zinc chloride, gave the known α-glucopyranose penta-acetate. Furthermore, the same mixture of aniline-*N*-glucoside tetra-acetates was obtained from α- or β-glucopyranose penta-acetate by hydrolysing the acetyl group from $C_{(1)}$ and treating the product with aniline (Frèrejacque, *Compt. rend.*, 1936,

202, 1190). This mixture of aniline-*N*-glucopyranoside tetra-acetates, while differing somewhat in melting range and specific rotation in different preparations, was invariably separable by fractional crystallisation or through the carbon tetrachloride complex of one of them (Frèrejacque, *loc. cit.*) into the two pure isomers. One of these, also obtained when acetobromoglucose reacts with aniline, is β-aniline-*N*-glucopyranoside, m. p. 97—98°, $[\alpha]_D^{18}$ $-57°$ (*c*, 0·4 in chloroform); the other is α-aniline-*N*-glucopyranoside tetra-acetate, m. p. 149—150°, $[\alpha]_D^{18}$ $+179°$ (*c*, 0·4 in chloroform). When the β-form is kept in methanol containing a trace of aqueous ammonia at room temperature it is slowly converted into the less soluble α-anomer. All the tetra-acetates mentioned here are deacetylated by methanol containing aqueous ammonia to the same aniline-*N*-glucoside which is obtained by direct condensation. These experiments show that aniline-*N*-glucoside is a mixture which reacts, when acetylated in pyridine, in the pyranose form only. It would appear probable although not certain, therefore, that the aniline-*N*-glucosides mentioned are mixtures of α- and β-aniline-*N*-glucopyranoside. These reactions are summarised in the annexed chart.


Glucose + Aniline
Aniline-*N*-glucoside
β-Glucopyranose penta-acetate
α- + β-Aniline-*N*-glucopyranoside tetra-acetate
Acetobromoglucose
β-Aniline-*N*-glucopyranoside tetra-acetate
α-Aniline-*N*-glucopyranoside tetra-acetate
α-Glucopyranose penta-acetate

When *p*-toluidine is used instead of aniline rather different results are obtained. Thus, although prepared by different workers by different methods, only one *p*-toluidine-*N*-glucoside has been isolated which has well-defined crystalline form and sharp melting point. Acetylation of this glucoside has now been found to give a single tetra-acetate, m. p. 145—146°, $[\alpha]_D^{18}$ $-34·2°$ in chloroform, which must be a derivative of β-*p*-toluidine-*N*-glucopyranoside, since it is identical with the compound prepared from acetobromoglucose and *p*-toluidine.

Although *p*-toluidine-*N*-glucoside is more stable than the corresponding aniline compound they both decompose on storage at room temperature. After about a year in specimen tubes both substances have decomposed to black tars. However, the tetra-acetates of both are stable at room temperature.

In all the cases recorded so far aniline- and *p*-toluidine-*N*-glucosides react to give derivatives with the pyranose ring-structure.

EXPERIMENTAL.

(The light petroleum used throughout had boiling range 60—80°.)

*Aniline-*N*-glucoside.*—Glucose (18 g., 1 mol.) was refluxed in absolute alcohol (150 ml.) with freshly re-distilled aniline (9·3 g., 1 mol.) for 2 hours. On cooling, a solid separated and was collected. This was recrystallised from absolute alcohol and washed with dry ether before being dried in an evacuated desiccator at room temperature. The almost white solid (15 g.), $[\alpha]_D^{18}$ $+5·1° \longrightarrow -51·7°$ (after 24 hours) (*c*, 1·6 in methanol), melted with decomposition at temperatures varying between 110° and 150°, depending on the rate of heating. A further crop of product (6 g.), $[\alpha]_D^{18}$ $+11·25° \longrightarrow -51·9°$ (after 24 hours) (*c*, 0·4 in methanol), was obtained by partial concentration of the reaction mother-liquor. Further concentration gave more product (3 g.), $[\alpha]_D^{18}$ $+5° \longrightarrow -52·3°$ (total yield, 95%). Irvine and Gilmour give $[\alpha]_D$ $+10° \longrightarrow -52°$ for the first fraction and $[\alpha]_D$ $-20·1° \longrightarrow -52°$ for later fractions.

Glucose (5 g., 1 mol.) in absolute alcohol (15 ml.) and water (5 ml.) was left at room temperature for a week with aniline (8 g., 3 mols.). The solution was then evaporated to dryness over silica gel in an evacuated desiccator. The solid was purified by repeated washing with cold absolute alcohol and then with ether and dried as above. The appearance of the product (4 g., 53%), $[\alpha]_D^{18}$ $+6° \longrightarrow -52·3°$ (*c*, 0·4 in methanol), was similar to the previous one.

Aniline-*N*-glucoside, prepared by the method of Weygand (*loc. cit.*), was a cream-coloured powder,

$[\alpha]_D^{18}$ +10·3 $\longrightarrow$ −52·5° (*c*, 0·4 in methanol). Weygand gives m. p. 140°, but does not mention the specific rotation. This method was the normal one used hereafter for preparing aniline-*N*-glucoside.

The solid products were examined microscopically under polarized light and were seen to be non-crystalline.

Mutarotation of Aniline-N-*glucoside.*—The mutarotation of aniline-*N*-glucoside in methanol and ethanol proceeds smoothly. In dry pyridine no change in rotation takes place but rapid mutarotation in pyridine–acetic acid was observed. The following values were obtained: $[\alpha]_D^{16}$ −12·5° (*c*, 2·0 in pyridine); $[\alpha]_D^{16}$ −11·3° $\longrightarrow$ −62·5° (after 24 hours) (*c*, 0·4 in pyridine containing a trace of glacial acetic acid); $[\alpha]_D^{16}$ $\longrightarrow$ −60·0° (equilibrium value after 6 minutes) (*c*, 0·8 in pyridine, 66 ml.; acetic acid 34 ml.).

Aniline-*N*-glucoside, $[\alpha]_D^{16}$ +10·5° $\longrightarrow$ −52·5° (*c*, 0·8 in methanol), was recovered by allowing the methanolic solution to evaporate at room temperature.

Acetylation of Aniline-N-*glucoside.*—Aniline-*N*-glucoside (20 g.) was dissolved in pyridine, and acetic anhydride (80 ml.) was added gradually at 0°. After 24 hours at room temperature the pyridine solution was poured on ice. After several hours the product was filtered off, washed with water, and dried in a vacuum at room temperature. The crude crystals (23 g., 64%), m. p. 80—85°, were recrystallised from absolute alcohol–light petroleum. During this recrystallisation an oil separated first, followed by a larger crop of crystals, m. p. 92—105°, $[\alpha]_D^{16}$ +40·2° (*c*, 2·5 in chloroform). These, after several recrystallisations, were a mixture of aniline-*N*-glucoside tetra-acetates, m. p. 88·5—92·5°, $[\alpha]_D^{16}$ +45·8° (*c*, 2·5 in chloroform) (Found: C, 56·4; H, 5·9; N, 3·3. $C_{20}H_{25}O_9N$ requires C, 56·7; H, 5·95; N, 3·3%). The oil which separated during the recrystallisation subsequently solidified and was purified by recrystallisation from a small volume of methanol and then from absolute alcohol–light petroleum. This product, which was subsequently proved to be *α-aniline*-N-*glucopyranoside tetra-acetate*, was a single substance, m. p. 149—150°, $[\alpha]_D^{16}$ +180° (*c*, 2·5 in chloroform) (Found: C, 56·9; H, 6·0; N, 3·3%).

The product of another acetylation was separated by the method of Frèrejacque (*loc. cit.*). Aniline-*N*-glucoside tetra-acetate, m. p. 88—92·5°, $[\alpha]_D^{16}$ +45·7° (10 g.), was separated into *β*- (6 g., 60%), m. p. 97—98°, $[\alpha]_D^{16}$ −57° (*c*, 0·4 in chloroform), $[\alpha]_D^{16}$ −68·3° (*c*, 0·4 in 90% aqueous alcohol) and *α*-aniline-*N*-glucopyranoside tetra-acetate (4 g., 40%), m. p. 149—150°, $[\alpha]_D^{16}$ +179° (*c*, 0·4 in chloroform).

In another experiment aniline-*N*-glucoside (5 g.) was heated on a water-bath in pyridine (20 ml.) and acetic anhydride (20 ml.). After 20 minutes' heating the solution was allowed to cool and left overnight at room temperature. The product was isolated as in the previous preparation, and after recrystallisations from alcohol–light petroleum it was shown similarly to be a mixture of *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates (5 g., 62%), m. p. 92—110°, $[\alpha]_D^{16}$ +55·3° (*c*, 2·4 in chloroform).

A similar product was obtained by treating aniline-*N*-glucoside for 30 minutes in pyridine with acetic anhydride in the presence of a small amount of perchloric acid.

In another experiment the lævorotatory form of aniline-*N*-glucoside was acetylated. Aniline-*N*-glucoside (5 g.) in pyridine (20 ml.) containing acetic acid (0·5 ml.) was kept at room temperature for 3 days before addition of acetic anhydride (20 ml.) at 0°. After a further day at room temperature the product was isolated as before. After recrystallisations from alcohol–light petroleum there remained a mixture of *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates (5 g., 62%), m. p. 88—95°, $[\alpha]_D^{16}$ +67·4° (*c*, 0·8 in chloroform).

Conversion of β- into α-Aniline-N-*glucopyranoside Tetra-acetate.*—If a saturated solution of any of the above mixed *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates, or of the pure *β*-anomer, in methanol containing a drop of aqueous ammonia (10%) was kept at room temperature, then a gradual separation of crystalline material took place. This material, on recrystallisation, was found to be *α*-aniline-*N*-glucopyranoside tetra-acetate (80% yield), m. p. 149—150°, $[\alpha]_D^{16}$ +180° (*c*, 0·4 in chloroform).

Conversion of Aniline-N-*glucopyranoside Tetra-acetates into α-Glucopyranose Penta-acetate.*—The hydrolysis of aniline-*N*-glucopyranoside tetra-acetates was successfully achieved by the method of Berger and Lee (*loc. cit.*). The crude glucose tetra-acetate was obtained as a viscous red syrup (3·5 g., 87%) which did not crystallise. This syrup (2 g.) was heated on a boiling-water bath for 30 minutes with acetic anhydride (25 ml.) and powdered anhydrous zinc chloride (0·5 g.). After being poured into water and kept for several hours the product was extracted with chloroform. The extract was washed free from acid and dried before the chloroform was evaporated off, leaving a syrup which crystallised from alcohol. The product was *α*-glucopyranose penta-acetate (1·7 g., 78%), m. p. 110—111°, $[\alpha]_D^{16}$ +100·9°. A mixed m. p. with authentic *α*-glucopyranose penta-acetate, m. p. 110—111°, showed no depression.

Preparation of Aniline-N-*glucopyranoside Tetra-acetates from β-Glucopyranose Penta-acetate.*—The method of Frèrejacque (*loc. cit.*) was used. The product was recrystallised from alcohol–light petroleum and was a mixture of *α*- and *β*-aniline-*N*-glucopyranoside tetra-acetates, m. p. 88—92·5°, $[\alpha]_D^{16}$ +46·1° (*c*, 0·9 in chloroform). This mixture was separated by the procedure already described into *α*-aniline-*N*-glucopyranoside tetra-acetate and the corresponding *β*-anomer.

Preparation of β-Aniline-N-*glucopyranoside Tetra-acetate from Acetobromoglucose.*—The method of Baker (*J.*, 1928, 1583) was used. After recrystallisation from ether–light petroleum there was obtained pure *β*-aniline-*N*-glucopyranoside tetra-acetate, m. p. 96—97°, $[\alpha]_D^{16}$ −70·3° (*c*, 0·4 in 90% alcohol), $[\alpha]_D^{16}$ −55° (*c*, 0·4 in chloroform). Baker (*loc. cit.*) gives m. p. 98°, $[\alpha]_D^{16}$ −73·3° (in 90% alcohol).

Deacetylation of Aniline-N-*glucopyranoside Tetra-acetates.*—The standard procedure was to allow the tetra-acetate (4 g.) to remain in methanol (40 ml.) containing aqueous ammonia (5 ml., *d* 0·880) at room temperature for 3 days. After removal of the solvent at room temperature under reduced pressure the product was purified by recrystallisation from alcohol. In different experiments. *α*-aniline-*N*-glucopyranoside tetra-acetate, the *β*-anomer, and mixtures of *α*- and *β*-anomers were used. In each case aniline-*N*-glucoside was obtained: $[\alpha]_D^{18}$ *ca.* +10° $\longrightarrow$ −52° (in methanol), *i.e.*, identical with the substance prepared directly from glucose and aniline.

p-*Toluidine*-N-*glucoside.*—Glucose (5·4 g., 1 mol.) was heated with *p*-toluidine (3·2 g., 1 mol.) and water (1 ml.) on a boiling-water bath until homogeneous (15 minutes). Ether (100 ml.) was added and the precipitated solid (6 g., 86%) filtered off. Recrystallisation from ether–alcohol gave needle-shaped crystals of *p*-toluidine-*N*-glucoside, m. p. 117—118°, $[\alpha]_D^{24}$ −101·2° $\longrightarrow$ −45·8° (*c*, 0·5 in methanol).

This same compound has been obtained by different procedures by Irvine and Gilmour (*J.*, 1909, **95**, 1548) and Kuhn and Dansi (*Ber.*, 1936, **69**, 1745).

*β-*p*-Toluidine-*N*-glucopyranoside Tetra-acetate.*—β-*p*-Toluidine-*N*-glucoside tetra-acetate was prepared from acetobromoglucose by the method of Baker (*loc. cit.*). After recrystallisation from absolute alcohol pure β-*p*-toluidine-*N*-glucopyranoside tetra-acetate was obtained, having m. p. 144—145°, $[\alpha]_D^{18}$ −33·4° (*c*, 0·4 in chloroform).

p-Toluidine-*N*-glucoside (5 g.) was dissolved in pyridine (20 ml.) and acetic anhydride (20 ml.) at 0°. After 24 hours at room temperature the solution was poured on ice. After several hours the solid product was collected and recrystallised from alcohol. This was β-*p*-toluidine-*N*-glucopyranoside tetra-acetate (5 g., 70%), m. p. 145—146°, $[\alpha]_D^{16}$ −34·2° (*c*, 0·5 in chloroform), mixed m. p. with the compound prepared above, 144—145°. For this compound Kuhn and Dansi (*loc. cit.*) cite m.p. 144—145°, $[\alpha]_D^{18}$ −57·5° (in methyl acetate).

UNIVERSITY OF LONDON, KING'S COLLEGE. [*Received, December 19th*, 1949.]

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200. *Experiments on the Synthesis of the Pyrethrins. Part III. Synthesis of Dihydrocinerin-I and Tetrahydropyrethrin-I; a Study of the Action of* N*-Bromosuccinimide on 3-Methyl-2-*n*-alkyl (and alkenyl)-*cyclo*pent-2-en-1-ones.*

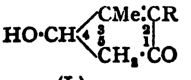
By LESLIE CROMBIE, MICHAEL ELLIOTT, and STANLEY H. HARPER.

3-Methyl-2-*n*-alkyl*cyclo*pent-2-en-1-ones with one molecular proportion of *N*-bromosuccinimide undergo monosubstitution at the 4-position, together with some disubstitution (probably at the 4- and the 1′-position), and hence recovery of unchanged ketone. The bromoketone is converted into the acetoxyketone, which is hydrolysed to the (±)-4-hydroxy-3-methyl-2-*n*-alkyl*cyclo*pent-2-en-1-one. By this means are prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone (alkyl being butyl and amyl respectively), transformation products of cinerolone and of pyrethrolone, the alcoholic components of the natural pyrethrins. The bromoketones and silver (±)-*trans*-chrysanthemate give racemic dihydrocinerin-I and tetrahydropyrethrin-I which have very little insecticidal action.

The bromo-ketones readily eliminate hydrogen bromide, *e.g.*, with organic bases or sodium methoxide, to give *cyclo*pentadienones, characterised by high-melting derivatives but themselves probably existing only as dimers.

3-Methyl-2-*n*-alkenyl*cyclo*pent-2-en-1-ones undergo preferential side-chain substitution with *N*-bromosuccinimide, followed by elimination of hydrogen bromide and polymerisation. 3-Methyl-2-*n*-pent-4′-enyl*cyclo*pent-2-en-1-one undergoes very ready disubstitution, followed by elimination of hydrogen bromide. No monomeric product apart from unchanged ketone could be isolated and the method fails as a route to pyrethrolone or cinerolone and analogues containing alkenyl side chains.

THE erroneous formulation of pyrethrolone (I*a*) as an α-ketol, with the hydroxyl group in the 5-position, was founded on its reducing properties and the isolation of a supposed *p*-nitrophenylosazone by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 212). Subsequently, by analogy, cinerolone (I*b*) was also formulated as an α-ketol (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114). However, LaForge and Soloway (*J. Amer. Chem. Soc.*, 1947, **69**, 186, 2932) showed that synthetic (±)-5-hydroxy-3-methyl-2-*n*-butyl*cyclo*pent-2-en-1-one was not identical with naturally derived (±)-dihydrocinerolone and assigned the hydroxyl group to $C_{(4)}$, the only other vacant position in the ring. This structure (I*d*), with the hydroxyl group in an "allylic" position, accords well with the reactivity of the chloro-ketones obtained by the action of thionyl chloride on cinerolone, dihydrocinerolone, or tetrahydropyrethrolone, and with the ready hydrogenolysis of pyrethrolone acetate, pyrethrolone methyl ether, and the pyrethrins themselves. Further dihydrocinerolone possesses only feeble reducing power and does not yield a *p*-nitrophenylosazone, which excludes the α-ketol formulation.



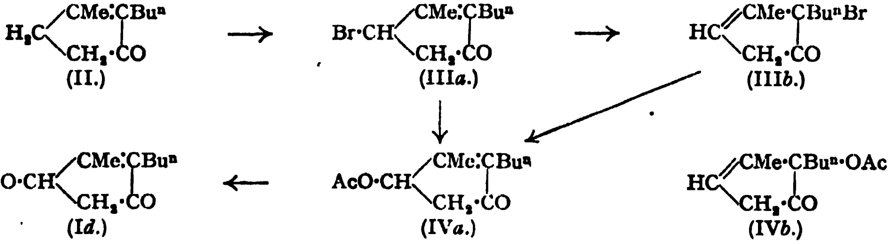
(I.)

I*a*, R = $\overset{1'}{C}H_2\cdot\overset{2'}{C}H{:}CH\cdot CH{:}CH_2$
I*b*, R = $CH_2\cdot CH{:}CHMe$
I*c*, R = $CH_2\cdot CH_2\cdot CH_2\cdot CH_2Me$
I*d*, R = $CH_2\cdot CH_2\cdot CH_2Me$

Some confirmation of the correctness of the proposed structure was obtained by Soloway and LaForge (*ibid.*, p. 979) who synthesised a ketol by refluxing dihydrocinerone with *N*-bromosuccinimide in carbon tetrachloride for 18 hours and hydrolysing the crude bromo-ketone with an aqueous suspension of chalk. The semicarbazone and 3 : 5-dinitrobenzoate of this ketol were identical (mixed melting points) with those from naturally derived (±)-dihydrocinerolone. This work was reported briefly without experimental details and no amplification has yet been published. Shortly afterwards Dauben and Wenkert (*ibid.*, p. 2075) described briefly the synthesis of the higher homologue, (±)-tetrahydropyrethrolone, by a similar route from tetrahydropyrethrone, but using only a 30-minutes reaction period and hydrolysing the bromo-ketone with an aqueous suspension of barium carbonate. They also prepared the acetoxy-ketone by reaction of the bromo-ketone with silver acetate.

This paper describes a study of the bromo-compounds obtained by the action of *N*-bromosuccinimide on dihydrocinerone, tetrahydropyrethrone, and related ketones, made in connection with the synthesis of racemic dihydrocinerin-I and tetrahydropyrethrin-I, during which we have prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone.

We found that dihydrocinerone reacted to completion in a few minutes with *N*-bromosuccinimide in boiling carbon tetrachloride, neither benzoyl peroxide nor ultra-violet irradiation being necessary. After removal of succinimide and solvent, the undistilled bromo-ketone was refluxed with silver acetate in glacial acetic acid. Fractional distillation of the product gave the *acetoxyketone* [(±)-*dihydrocineronyl acetate*] in 60% overall yield from dihydrocinerone. Since there was also a forerun of dihydrocinerone and the recovery of succinimide had been quantitative, it was suspected that di- or poly-bromination had occurred. This suspicion was confirmed, for the highest-boiling fraction had a carbon and a hydrogen content tending towards that calculated for a diacetoxy-ketone. Further, distillation of the bromination product resolved it into unchanged dihydrocinerone, *monobromodihydrocinerone* (the main product), intermediate fractions, and a final fraction with a bromine content approaching that calculated for a dibromodihydrocinerone. Dibromination, which was not mentioned by Soloway and LaForge or by Dauben and Wenkert, is not surprising since two allylic methylene groups (the 4 and 1′) are available for free-radical substitution. Attempts to hydrolyse the acetoxy-ketone by prolonged refluxing with aqueous suspensions of barium carbonate were not successful (contrast Dauben and Wenkert above), but brief hydrolysis with methanolic potassium hydroxide gave (±)-dihydrocinerolone which was characterised as its semicarbazone and 3 : 5-dinitrobenzoate. The overall yield from ketone to ketol was 44%.



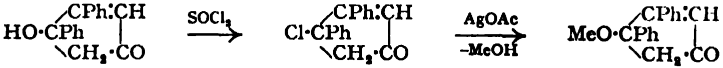
Similarly, tetrahydropyrethrone reacted rapidly and smoothly with one molecular proportion of *N*-bromosuccinimide, and the undistilled bromo-ketone gave, as above, tetrahydropyrethronyl acetate and (±)-tetrahydropyrethrolone, which was similarly characterised. This product did not react with lead tetra-acetate in acetic acid in the presence of water and is not therefore an α-ketol (cf. Baer and West, *J.*, 1949, 93). We also found that tetrahydropyrethrone reacted smoothly and completely with two molecular proportions of *N*-bromosuccinimide, without evolution of hydrogen bromide, and the dibromo-ketone so obtained reacted with yet another molecular proportion of *N*-bromosuccinimide in the presence of a trace of benzoyl peroxide.

Comparison of the physical properties and derivatives of our synthetic hydroxy-ketones with those of the corresponding naturally derived compounds shows satisfactory concordance (see *Nature*, 1948, 162, 222) and in conjunction with the mixed melting points determined by Soloway and LaForge (*loc. cit.*) leaves no doubt as to the identity of our products with naturally derived (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone.

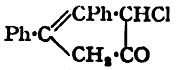
In the communications of Soloway and LaForge (*loc. cit.*) and of Dauben and Wenkert (*loc. cit.*) no conclusive evidence or reasoned argument was given to support the assumption that bromination occurs in the 4-position of the ring and that the resultant ketols are 4-hydroxy-3-methyl-2-alkyl*cyclo*pent-2-en-1-ones. We have shown that substitution can occur in more than one position. Apart from the 4-methylene group, as pointed out above, the 1′-methylene group should be prone to substitution by free-radical reagents, while substitution at the 3-methyl group and at the 5-methylene group is conceivable though less likely. Strong evidence against the hydroxy-group derived from bromination with one molecular proportion of *N*-bromosuccinimide being elsewhere than at $C_{(4)}$ has been adduced (Harper, *Ann. Reports*, 1948, 45, 162). The

4-hydroxy-structure of (±)-dihydrocinerolone has since been directly proved by synthesis: the cyclisation of (±)-3-hydroxy-*n*-decane-2 : 5-dione gives a product identical with the naturally derived material and with the ketol prepared by the *N*-bromosuccinimide route (mixed melting points of the 3 : 5-dinitrobenzoates) (Schechter, Green, and LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 3165; Crombie, Edgar, Harper, and Lowe, forthcoming publication). Although this establishes that bromination occurs initially at the 4-methylene group, it does not follow that the following stages necessarily take the direct course (II ⟶ III*a* ⟶ IV*a* ⟶ I*d*): there is a known tendency for the products of *N*-bromosuccinimide substitution to undergo allylic rearrangements (III*a* ⟶ III*b*), and for anionotropic rearrangement to occur (III*a* ⟶ IV*b*, or III*b* ⟶ IV*a*) on subsequent conversion into the acetoxy-ketones. That the acetoxy-ketone has the structure (IV*a*) is shown by its identity with naturally derived (±)-dihydrocineronyl acetate, prepared by catalytic reduction of (±)-cineronyl acetate which has been proved spectroscopically to contain an αβ-unsaturated carbonyl group (West, *J.*, 1946, 463). It is also known that in the alkaline hydrolysis of such esters, through acyl–oxygen fission, no rearrangement occurs. Any scheme involving (IV*b*) is therefore excluded.

The evidence excluding the participation of (III*b*) is less conclusive. LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 222) converted (±)-dihydrocinerolone by thionyl chloride into a chloro-ketone, and dehalogenation of this with zinc in ethanol gave the unrearranged ketone, dihydrocinerone (II). If this is the reverse of the direct hydrolysis of the bromo-ketone to (±)-dihydrocinerolone (Soloway and LaForge, *loc. cit.*), then participation of (III*b*) is unlikely. No closely analogous system has been investigated in detail. Burton and Shoppee (*J.*, 1934, 201; cf. Allen and Spanagel, *J. Amer. Chem. Soc.*, 1932, **54**, 4338; Burton, Shoppee, and Wilson, *J.*, 1932, 720) carried out the reactions (VI ⟶ V ⟶ VII) and did not detect any tendency for reaction as the rearranged form (VIII), although conversion into the acetate was not investigated. Roberts, Young, and Winstein (*J. Amer. Chem. Soc.*, 1942, **64**, 2157) found that 1- and 3-methylallyl chlorides were converted by silver acetate in acetic acid, mainly by a S_N1 mechanism, into similar mixtures of acetates in which the primary acetate predominated. Subsequently Young and Andrews (*ibid.*, 1944, **66**, 421) found that on the alkaline hydrolysis in aqueous ethanol the primary chloride reacted mainly by a S_N2 mechanism to give predominantly the primary alcohol, whereas the secondary chloride reacted mainly by a S_N1 mechanism to give a mixed product. We consider that bromodihydrocinerone is predominantly (III*a*); this is consistent with the exclusive formation of (I*d*) on direct hydrolysis and with the deep-red colour of the 2 : 4-dinitrophenylhydrazone formed by bromotetrahydropyrethrone, indicative of αβ-unsaturation to the carbonyl group. Nevertheless the mechanism of the reaction with acetate ion, and presumably other carboxylate ions, is such that some (III*b*) could be present without detriment to the purity of the product.

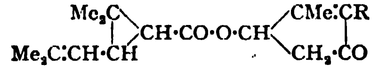


(VI.) (V.) (VII.)

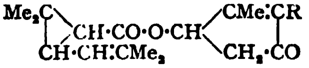


(VIII.)

Our main objective, the synthesis of racemic *dihydrocinerin*-I and *tetrahydropyrethrin*-I, was effected by refluxing bromodihydrocinerone and bromotetrahydropyrethrone respectively with silver (±)-*trans*-chrysanthemate (Campbell and Harper, *J.*, 1945, 283) in carbon tetra-



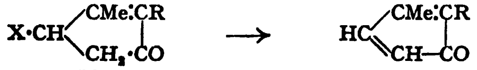
(IX.)



(X.)

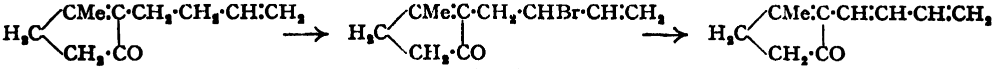
		% Knock-down, 10 minutes' exposure.	% Kill, 24 hours.
(±)-*n*-Butylrethronyl (±)-*trans*-chrysanthemate (racemic dihydrocinerin-I)	(IX; R = Buⁿ)	25	3·6
(±)-*n*-Butylrethronyl (±)-*cis*-chrysanthemate	(X; R = Buⁿ)	15	3·8
(±)-*n*-Amylrethronyl (±)-*trans*-chrysanthemate (racemic tetrahydropyrethrin-I)	(IX; R = C_5H_{11}-*n*)	0	0·9
(±)-*n*-Amylrethronyl (±)-*cis*-chrysanthemate	(X; R = C_5H_{11}-*n*)	0	2·9
Official Test Insecticide	—	100 (in 3 mins.)	56·0 (mean of 3)
Odourless distillate alone	—	0	2·0
Unsprayed control	—	—	0·6 (mean of 6)

chloride. In a similar manner esters from (±)-*cis*-chrysanthemic acid (Campbell and Harper, *loc. cit.*) were prepared (see Table) (for an exposition of the nomenclature for these esters, see Harper, *Chem. and Ind.*, 1949, 636). These esters at a concentration of 0·5% w/v in refined kerosene ("odourless distillate" used as a spray base) have been tested for insecticidal activity against house-flies by Dr. E. A. Parkin and Mr. A. A. Green of the Insecticides Section, Pest Infestation Laboratory, with the results summarised in the Table. The values are those of a single spraying, using a 10-minutes' exposure in the spray chamber, by the standardised procedure of the Pest Infestation Laboratory (Parkin and Green, *Nature*, 1944, **154**, 16) and comparison is made with the Official Test Insecticide containing 0·1% w/v natural pyrethrins. Although the esters derived from dihydrocinerolone show slight knock-down, all give negligible kill. Such results are in accord with the low toxicity observed by Haller and Sullivan (*J. Econ. Entomol.*, 1938, **31**, 276) for hydrogenated natural pyrethrin-I, by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 448) and by Gersdorff (*J. Econ. Entomol.*, 1947, **40**, 878) for (+)-*n*-amylrethronyl (+)-*trans*-chrysanthemate resynthesised from naturally derived acid and hydrogenated alcohol The double bonds in the side chains of the natural pyrethrins are therefore of great importance for insecticidal activity.

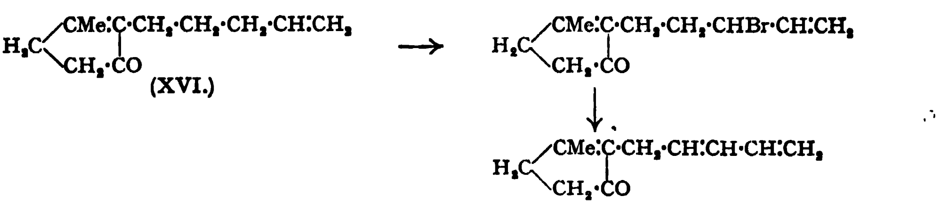


(XI.) (XII.)

Structures of the type of (XI) would be expected to eliminate HX with ease to give compounds which are formulated tentatively as *cyclo*pentadienones (XII) or their dimers. Thus Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 226) record that pyrethronyl acetate eliminates acetic acid on pyrolysis, and on distillation the pyrethrins themselves give a lower-boiling fraction. When the synthetic esters described above were distilled, a forerun of chrysanthemic acid was obtained and characterised as its *p*-phenylphenacyl ester. This was not due to the presence of free acid in the crude product since the silver salt would not have hydrolysed under the conditions of the reaction and prolonged heating of the silver salt in a vacuum gave no volatile product. Treatment of bromodihydrocinerone with anhydrous trimethylamine in benzene and warming the quaternary salt thus formed with an aqueous suspension of magnesium oxide eliminated 90% of the bromine as trimethylammonium bromide. The resulting *cyclo*pentadienone (XII; R = Bu^n) would be expected to exist in a dimeric form but yield monomeric derivatives. A *semicarbazone* (m. p. 227°) and a deep-red 2 : 4-*dinitrophenylhydrazone* were isolated in good yield and gave analytical values consitent with their being derivatives of 3-methyl-2-*n*-butyl*cyclo*penta-2 : 4-dien-1-one. Similarly bromotetrahydropyrethrone with methanolic sodium methoxide gave no methyl ether but 83% of the bromine was eliminated as hydrogen bromide to give a product yielding a *semicarbazone* (m. p. 219°), presumably of



(XIII.) (XIV.) (XV.)



(XVI.) (XVII.)

3-methyl-2-*n*-amyl*cyclo*penta-2 : 4-dien-1-one. This semicarbazone is probably identical with that (m. p. 220°) which Staudinger and Ruzicka (*loc. cit.*) obtained from tetrahydropyrethrolone semicarbazone and regarded as being derived through heterocyclisation by elimination of water from the α-hydroxy-group.

Less success attended attempts to monobrominate, in the 4-position, *cyclo*pentenones related more closely to cinerone and pyrethrone in that they contained alkenyl side-chains. 3-Methyl-2-*n*-but-3′-enyl*cyclo*pent-2-en-1-one (XIII) reacted smoothly with one molecular proportion of *N*-bromosuccinimide, but after 15 minutes evolution of hydrogen bromide commenced. The sole product isolated by distillation was unchanged ketone (~15%) together with a non-volatile polymeric residue. Evidently preferential substitution occurs at the 2′-methylene up adjacent to the side-chain double bond, together with some disubstitution, possibly at the sition. Elimination of hydrogen bromide from (XIV) would lead to a cross-conjugated trienone (XV) which might be expected to polymerise. Attention was then directed to 3-methyl-*n*-pent-4′-enyl*cyclo*pent-2-en-1-one (XVI) (the preparation of this ketone will be described in a forthcoming communication), for in this case preferential side-chain substitution at the 3′-position followed by elimination of hydrogen bromide could lead to pyrethrone (XVII) and thence, with substitution at the 4-position, possibly to pyrethrolone (I*a*) itself. After reaction with one molecular proportion of *N*-bromosuccinimide (again hydrogen bromide was evolved), only unchanged ketone (48%) could be isolated: no monosubstitution occurred, but all the ketone that reacted underwent dibromination. On the assumption that any bromopyrethrone present might polymerise on distillation, the undistilled bromo-ketone was treated with silver acetate in glacial acetic acid and the product converted into the semicarbazone; again only the derivative of the starting ketone was obtained, with no indication of the presence of pyrethronyl acetate semicarbazone. The side-chain double bond was blocked by the addition of bromine and the product treated with *N*-bromosuccinimide, but reagents used to eliminate vicinal bromine atoms also attacked the labile bromine at position 4. The *N*-bromosuccinimide route is therefore incapable of extension to the preparation of ketols containing alkenyl side chains.

EXPERIMENTAL.

Microanalyses, other than bromine determinations, were carried out by Drs. Weiler and Strauss, Oxford.

Reaction of Dihydrocinerone with N-*Bromosuccinimide.*—Dihydrocinerone (3·19 g.) (regenerated from the semicarbazone; b. p. 113°/15 mm., n_D^{25} 1·4802; cf. Harper, *J.*, 1946, 892) and *N*-bromosuccinimide (3·75 g., 1·0 mol.) were heated to boiling in carbon tetrachloride (10 ml.). Reaction commenced, as shown by a marked increase in the rate of reflux and succinimide floating to the surface, within 5 to 10 minutes and was completed by a further 15—30-minutes' refluxing. In other experiments neither the addition of catalytic quantities of benzoyl peroxide nor the use of freshly recrystallised *N*-bromosuccinimide caused any significant variation. The suspension was cooled to 0° and the succinimide collected (2·09 g., 99·5%). The carbon tetrachloride was removed from the filtrate by distillation through a short column at atmospheric pressure and the residue kept over paraffin wax in a vacuum desiccator, to give the crude bromo-ketone (5·52 g., 98%), n_D^{20} 1·5177. In another experiment the crude bromo-ketone (4·08 g.) was distilled at *ca.* 5 × 10^{-3} mm. through a plain column (220 × 6 mm.), both the flask and column being immersed in an oil-bath, to give the fractions: (i) b. p. 42—46° (0·21 g.); (ii) b. p. 47—56°, n_D^{25} 1·5132 (0·78 g.); (iii) b. p. 56—63°, n_D^{25} 1·5193 (1·69 g.) (Found: Br, 33·9. $C_{10}H_{15}OBr$ requires Br, 34·6%); (iv) b. p. 63—70° (0·62 g.); and (v) b. p. 85—88° (0·44 g.) (Found: Br, 45·4. $C_{10}H_{14}OBr_2$ requires Br, 51·5%). Fraction (i) consisted of unchanged ketone and the recovery of this together with the quantitative recovery of succinimide is consistent with the presence of dibromodihydrocinerone in (v). The spread of b. p. of fractions (ii)—(iv) of the *monobromodihydrocinerone* was caused, in part at least, by fluctuation of pressure but does not entirely exclude heterogeneity of the product.

Hydrolysis of Bromodihydrocinerone.—In early experiments, carried out in 1946, direct hydrolysis of the undistilled bromo-ketone was attempted by refluxing it with aqueous potassium carbonate. This procedure yielded a bromine-free product, boiling in the correct range for dihydrocinerolone, which it was attempted to characterise as semicarbazone. However, only small quantities of impure derivative were obtained which could not be satisfactorily purified. Later experience showed that even when pure ketol is used the semicarbazone is formed and isolated with difficulty and only in low yield. It is likely therefore that (±)-dihydrocinerolone was actually obtained in these experiments.

The undistilled bromo-ketone (4·50 g.) and powdered silver acetate (7·5 g.) were refluxed in glacial acetic acid (25 ml.) for 4 hours. Next day the silver bromide was filtered off (3·08 g., after being washed with dilute nitric acid, equiv. to only 83·5% reaction) and the acetic acid removed by distillation through a short column under slightly reduced pressure. Distillation of the residue yielded, after a small forerun, *acetoxydihydrocinerone* [(±)-*dihydrocineronyl acetate*] (2·47 g., 60%), b. p. 100—103° (mainly 101°)/0·75 mm., n_D^{20} 1·4772 (Found: C, 68·2; H, 9·2. $C_{12}H_{18}O_3$ requires C, 68·2; H, 8·6%). The semicarbazone, prepared in the cold, had m. p. 148° not clearing until 163°, but could not be satisfactorily purified. The red 2 : 4-dinitrophenylhydrazone when prepared in cold alcoholic hydrochloric acid and crystallised from methanol had m p. 125—126°, but when prepared in boiling alcoholic hydrochloric acid and crystallised from ethanol or Cellosolve (methyl ether) had m. p. 136—137°. In another experiment, with 2·60 g. of undistilled bromo-ketone, the product was fractionally distilled at 0·3 mm. to give the fractions: (i) b. p. 63—69°, n_D^{20} 1·4810 (80 mg.) (Found: C, 75·9; H, 10·5. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%); (ii) b. p. 87—88°, n_D^{20} 1·4770 (760 mg.) (Found: C, 68·6; H, 8·9. $C_{12}H_{18}O_3$ requires C, 68·2; H, 8·6%); (iii) b. p. 89—92°, n_D^{20} 1·4775 (180 mg.) (Found: C, 68·2; H, 8·5%); (iv) b. p. 95°, n_D^{20} 1·4778 (310 mg.); and (v) b. p. 129—131° (210 mg.) (Found: C, 65·4; H, 8·2. $C_{14}H_{20}O_5$ requires C, 62·6; H, 7·5%). Fraction (i) contained unchanged ketone which it was shown above is present in undistilled bromo-ketone. Fractions (ii)—(iv) consisted of the *monoacetoxy-ketone*, there being no indication of heterogeneity. Fraction (v) contained *diacetoxydihydrocinerone* derived from the small proportion of dibromoketone formed in the initial substitution.

Acetoxydihydrocinerone (1·63 g.) was hydrolysed by being refluxed with excess of 0·5N-methanolic potassium hydroxide and following the course of the reaction by back-titration at 20-minute intervals.

After 60 minutes hydrolysis was 95% complete and the methanol was removed through a column. Ether-extraction of the oily suspension, drying, and distillation yielded, after a small forerun, (±)-dihydrocinerolone (0·95 g., 73%), b. p. 114—117°/0·8 mm., n_D^{20} 1·4942; Soloway and LaForge (*J. Amer. Chem. Soc.*, 1947, **69**, 979) record b. p. 110—114°/0·3 mm., n_D^{25} 1·4955, for their synthetic ketol; LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 222) record b. p. 115—117°/1 mm., n_D^{22} 1·4958, for "natural" material. The 3 : 5-dinitrobenzoate, triturated with light petroleum and crystallised twice from ethanol, had m. p. 110—110·5° (Found: C, 56·3; H, 5·0. Calc. for $C_{17}H_{18}O_8N_2$: C, 55·5; H, 4·9%); Soloway and LaForge (*loc. cit.*) record m. p. 111° for their synthetic derivative and m. p. 111° for the "natural" ester. The semicarbazone had m. p. 184—185°; Soloway and LaForge (*loc. cit.*) record m. p. 187° for their synthetic derivative; LaForge and Barthel (*loc. cit.*) record m. p. 185°; and West (*J.*, 1946, 463) records 184—185° for the naturally derived (±)-semicarbazone.

Reaction of Tetrahydropyrethrone with N-*Bromosuccinimide.*—Tetrahydropyrethrone (4·47 g.) (regenerated from the semicarbazone; b. p. 82·5°/0·7 mm., n_D^{25} 1·4764) was brominated, by the above procedure, to give the crude bromo-ketone (6·6 g.) (2 : 4-dinitrophenylhydrazone, deep-red needles, m. p. 128—130°, from methanol).

Hydrolysis of Bromotetrahydropyrethrone.—The undistilled bromo-ketone (6·6 g.) was likewise treated with silver acetate (12·0 g.) in boiling glacial acetic acid (25 ml.), and the product fractionally distilled at 3 mm. to give the fractions: (i) b. p. 116·5—124°, n_D^{25} 1·4731 (0·24 g.); (ii) b. p. 124—129°, n_D^{25} 1·4755, (0·22 g.); (iii) b. p. 129—135°, n_D^{25} 1·4764 (0·33 g.); (iv) b. p. 135—140°, n_D^{25} 1·4750 (1·00 g.); (v) b. p. 140—144°, n_D^{25} 1·4745 (1·67 g.); (vi) b. p. 144—148°, n_D^{25} 1·4750 (0·86 g.); and (vii) b. p. 148—168°, n_D^{25} 1·4770 (0·38 g.). Fractions (iv)—(vi) were bulked and redistilled to give acetoxytetrahydropyrethrone [(±)-tetrahydropyrethronyl acetate] (3·01 g., 50% overall yield from tetrahydropyrethrone), b. p. 144—146°/3 mm., n_D^{25} 1·4747 (Found: C, 69·6; H, 9·5. Calc. for $C_{13}H_{20}O_3$: C, 69·6; H, 9·0%). Dauben and Wenkert (*J. Amer. Chem. Soc.*, 1947, **69**, 2075) record b. p. 120—123°/1 mm., n_D^{26} 1·4755, for their synthetic product; West (*J.*, 1945, 412) records b. p. 117°/1·3 mm., n_D^{20} 1·4761, for naturally derived (+)-acetate.

In another experiment, in an attempt to eliminate some of the manipulation, tetrahydropyrethrone (1·72 g.) was brominated with *N*-bromosuccinimide (1·85 g.) in carbon tetrachloride (15 ml.) and the separated succinimide filtered off. Silver acetate (1·0 g.) was added to the filtrate, and the suspension shaken at room temperature for 48 hours. After filtration and removal of the solvent the residue was fractionally distilled at 0·4 mm. to give the fractions: (i) b. p. 78—80°, n_D^{20} 1·4804 (120 mg.) (Found: C, 75·7; H, 10·0. Calc. for $C_{11}H_{18}O$: C, 79·4; H, 10·9%); (ii) b. p. 91—103°, n_D^{20} 1·4808 (150 mg.); (iii) b. p. 103°, n_D^{20} 1·4796 (260 mg.) (Found: C, 68·6; H, 9·0. Calc. for $C_{13}H_{20}O_3$: C, 69·6; H, 9·0%); (iv) b. p. 104°, n_D^{20} 1·4797 (130 mg.); and (v) b. p. 105°, n_D^{20} 1·4804 (140 mg.) (Found: C, 68·7; H, 9·15%). Fractions (i)—(ii) evidently contained unreacted tetrahydropyrethrone; fractions (iii)—(v) were pure acetoxytetrahydropyrethrone.

Although the acetoxy-ketone gave a deep-red 2 : 4-dinitrophenylhydrazone this could not be satisfactorily purified. The semicarbazone, which separated as an oil and only slowly solidified, had m. p. 132—132·5°, but there was insufficient for purification; Dauben and Wenkert (*loc. cit.*) record m. p. 85—86° for the semicarbazone, but this seems far too low, particularly as the naturally derived (+)-semicarbazone has m. p. 140—141° (West, *loc. cit.*).

In an attempt to hydrolyse acetoxytetrahydropyrethrone, the ester was recovered unchanged after 24 hours' refluxing with an aqueous-alcoholic suspension of barium carbonate. However, hydrolysis was achieved by refluxing the acetoxy-ketone (0·63 g.) with a slight excess of 0·5N-methanolic potasssium hydroxide for 1 hour. Extraction and distillation gave, after a small forerun, (±)-tetrahydropyrethrolone (0·25 g., 49%), b. p. 125—127°/0·4 mm., n_D^{25} 1·4882 (Found: C, 72·1; H, 9·9. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 10·0%); Dauben and Wenkert (*loc. cit.*) record b. p. 118—120°/0·3 mm., n_D^{25} 1·4921 for their synthetic ketol; West (*loc. cit.*) records b. p. 126—127°/0·8 mm., n_D^{20} 1·4932, for naturally derived (+)-ketol; LaForge and Barthel (*J Org. Chem.*, 1945, **10**, 114) record n_D^{28} 1·4900 and for (±)-tetrahydropyrethrolone, n_D^{28} 1·4892. The 3 : 5-dinitrobenzoate crystallised as needles with m. p. 105—106°; Dauben and Wenkert (*loc. cit.*) record m. p. 105—105·5° for the synthetic ester. The semicarbazone, crystallised from ethyl acetate, had m. p. 169°; Dauben and Wenkert (*loc. cit.*) record m. p. 170·2—170·6° for the synthetic semicarbazone; LaForge and Barthel (*loc. cit.*) record m. p. 172—173° and West (*J.*, 1946, 463) records m. p. 172—174° for the "natural" (±)-semicarbazone.

Preparation of Pyrethrins.—The (±)-*trans*-chrysanthemic acid used was prepared by Mr. H. W. B. Reed following the procedure of Campbell and Harper (*J.*, 1945, 283). When freshly prepared it had m. p. 54·0—54·5°, but when kept developed an unpleasant odour and softened before melting. This is characteristic of the *trans*-acid, whereas the (±)-*cis*-acid remains unchanged over a period of years. The (±)-*trans*-acid (2·02 g.) in alcohol was neutralised with approx. 0·1N-potassium hydroxide (phenolphthalein) and then rendered faintly acid with dilute nitric acid, a slight excess of aqueous ammonia added, and the solution boiled until neutral. The silver salt was precipitated with a slight excess of approx. 0·1N-silver nitrate, washed, and dried at 100° to a grey powder (3·02 g., 92%).

Silver (±)-*trans*-chrysanthemate (2·83 g., 1·1 mols.) was added to the filtered solution of bromodihydrocinerone in carbon tetrachloride (25 ml.), freshly prepared from dihydrocinerone (1·45 g.). The reaction mixture was kept at room temperature overnight, then refluxed for 30 minutes, filtered, and evaporated, and the residue was distiled at 10^{-3} mm. in a small flask with a short distillation path. The following fractions were obtained: (i) b. p. 65—72° (660 mg.); (ii) b. p. 105—121° (880 mg.); and (iii) b. p. 121—130° (580 mg.). Fraction (iii) was yellow because of decomposition towards the end of the distillation. Redistillation of fractions (ii) and (iii), after a small forerun, yielded (±)-n-*butylrethronyl* (±)-trans-*chrysanthemate* (*dihydrocinerin*-I), b. p. 114—115°/1 × 10^{-3} mm., n_D^{20} 1·4992 (890 mg., 29% overall) (Found: C, 74·75; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%). An attempt to characterise this keto-ester as a 4-phenylsemicarbazone failed. When fraction (i) was cooled to −80°, crystallisation started. The solid had m. p. 42—52° (Found: C, 71·1; H, 9·4. Calc. for $C_{10}H_{16}O_2$ C, 71·4; H, 9·6%). Its identity as (±)-*trans*-chrysanthemic acid was confirmed by preparation of the *p*-phenylphenacyl ester, m. p. 113·5—115°, not depressed on admixture with an authentic specimen (Campbell and Harper, *loc. cit.*). Although silver (±)-*trans*-chrysanthemate became black and formed a mirror when heated to

240° at 10^{-3} mm., no distillation occurred. It is evident that the acid obtained above was formed by pyrolysis of the ester.

Tetrahydropyrethrin-I was prepared similarly by bromination of tetrahydropyrethrone (1·0 g.) and reaction with silver (±)-*trans*-chrysanthemate (1·90 g.). Fractional distillation of the crude product at 10^{-3} mm. gave (i) b. p. 86—87° (440 mg.) (Found : C, 71·0; H, 9·55. Calc. for $C_{10}H_{16}O_2$: C, 71·4 : H, 9·6%), and (ii) b. p. 110—150° (770 mg.). Fraction (i) crystallised and was evidently (±)-*trans*-chrysanthemic acid. Redistillation of fraction (ii) with elimination of a small forerun (50 mg.), yielded (±)-n-*amylrethronyl* (±)-trans-*chrysanthemate* (*tetrahydropyrethrin-I*), b. p. 96°/7 × 10^{-4} mm., n_D^{20} 1·4970 (410 mg., 21% overall) (Found : C, 74·2; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%). The keto-ester gave a brick-red 2 : 4-dinitrophenylhydrazone crystallising after many recrystallisations from ethanol, as prisms, m. p. 167°.

(±)-*cis*-Chrysanthemic acid (1·02 g.) was dissolved in a slight excess of 2·5N-sodium hydroxide, and rendered slightly acid with dilute nitric acid and then just alkaline with ammonia. The silver salt was precipitated by a slight excess of approx. 0·1N-silver nitrate, washed, and dried at 100° (1·41 g., 87%).

By a similar procedure dihydrocinerone (700 mg.) was brominated and then treated with silver (±)-*cis*-chrysanthemate (1·18 g.). The product boiled mainly at 133—144°/3 × 10^{-3} mm., and crystals of (±)-*cis*-chrysanthemic acid separated on storage. A light-petroleum solution was therefore washed with sodium hydrogen carbonate, and the residual ester re-distilled, to give (±)-n-*butylrethronyl* (±)-cis-*chrysanthemate*, b. p. 117—119°/3 × 10^{-4} mm., n_D^{20} 1·5000 (560 mg., 38% overall) (Found : C, 74·1, 74·2; H, 9·6, 9·5. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%).

Tetrahydropyrethrone (740 mg.) was brominated and then treated with silver (±)-*cis*-chrysanthemate (1·28 g.). Distillation at 10^{-2} mm. gave fractions : (i) b. p. 63—95° (40 mg.), and (ii) b. p. 120—153° (900 mg.). Both fractions deposited crystals when kept, which after being rinsed with light petroleum had m. p. 109—113°, not depressed on admixture with authentic (±)-*cis*-chrysanthemic acid. The light-petroleum solution was washed with sodium hydrogen carbonate, dried, evaporated, and distilled, to give (±)-n-*amylrethronyl* (±)-cis-*chrysanthemate*, b. p. 120—124°/2 × 10^{-3} mm., n_D^{20} 1·4980 (640 mg., 43% overall) (Found : C, 74·9; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·5%).

Immediately after distillation portions of these esters were sealed under nitrogen for analysis and for insecticidal assay. Portions kept for nearly 2 years show no signs of deterioration.

Elimination of Hydrogen Bromide from Bromodihydrocinerone.—Anhydrous trimethylamine vapour was passed into a solution of the bromo-ketone (850 mg.; b. p. 56°/6 × 10^{-4} mm., n_D^{25} 1·5178) in dry thiophen-free benzene (10 ml.). There was an immediate precipitate of white crystals. The suspension was kept for 12 hours, and then more trimethylamine vapour was passed in to complete the reaction. Benzene was removed in a vacuum at 40°, a suspension of magnesium oxide (400 mg.) in a little water was added, and the suspension boiled for 30 minutes. The organic material was extracted with ether, and the extract divided into two portions after being dried. One portion of the ethereal extract was evaporated and the residue converted into the 2 : 4-*dinitrophenylhydrazone* in boiling alcoholic hydrochloric acid. It separated in two forms from Cellosolve (methyl ether)—a dark red form crystallising almost at once and an orange modification which separated only on long storage of the mother-liquor. Both formed dark red blades, m. p. 236°, from alcohol–nitrobenzene (Found : C, 58·75; H, 5·4; N, 16·6. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 16·95%). The other portion of the extract yielded, after 5 minutes' refluxing with semicarbazide hydrochloride in pyridine–ethanol solution, a semicarbazone, m. p. 227° (decomp.) (from Cellosolve) (Found : C, 63·1; H, 8·0. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3%). Attempts to characterise the 3-methyl-2-*n*-butyl*cyclo*penta-2 : 4-dien-1-one as its dimer were unsuccessful.

Elimination of Hydrogen Bromide from Bromotetrahydropyrethrone.—Undistilled bromo-ketone (500 mg.) was added to a cold solution of sodium (47 mg., 1 g.-atom) in methanol (5 ml.) and kept for 12 hours at room temperature. The orange solution was acidified and extracted with ether. The ethereal extract was evaporated and the residue converted into the *semicarbazone*, which formed microcrystalline needles (from Cellosolve), m. p. 219° (Found : C, 65·0; H, 8·95; N, 18·1. $C_{12}H_{19}ON_3$ requires C, 65·1; H, 8·65; N, 19·0%), and was evidently the derivative of 3-methyl-2-*n*-amyl*cyclo*penta-2 : 4-dien-1-one and not the methyl ether semicarbazone ($C_{13}H_{23}ON_3$ requires C, 61·6; H, 9·15; N, 16·5%)

Undistilled bromo-ketone (from 197 mg. of tetrahydropyrethrone) was refluxed with zinc dust (160 mg.) in ethanol (2 ml.) for 45 minutes. Addition of water and extraction with ether yielded a viscous product which was converted into the semicarbazone. This derivative separated quickly and after recrystallisation from Cellosolve had m. p. 221—223° not depressed on admixture with the above semicarbazone, m. p. 219°. Evidently elimination of hydrogen bromide occurred instead of reductive replacement of bromine to give tetrahydropyrethrone (semicarbazone, m. p. 177°), although LaForge and Haller (*J. Org. Chem.*, 1936, **1**, 38) were able to reduce chlorotetrahydropyrethrone to tetrahydropyrethrone by this method.

The bromo-ketone liberated iodine from potassium iodide in boiling ethanol.

*Reaction of 3-Methyl-2-*n*-but-3'-enyl*cyclo*pent-2-en-1-one with* N-*Bromosuccinimide.*—The ketone (1·20 g.) (regenerated from the semicarbazone; b. p. 129—133°/25 mm., n_D^{25} 1·4928; cf. Harper, *loc. cit.*) reacted smoothly with *N*-bromosuccinimide (1·42 g., 1·0 mol.) in boiling carbon tetrachloride (30 ml.). After 15 minutes evolution of hydrogen bromide was observed, and refluxing was continued until this was complete (*ca.* 1 hour). After filtration and evaporation of the solvent the viscous residue was distilled. The sole volatile product (160 mg.) had b. p. 50°/7 × 10^{-2} mm. and gave a 2 : 4-dinitrophenylhydrazone, crystallising from ethanol in red needles, m. p. 145°, not depressed on admixture with the 2 : 4-dinitrophenylhydrazone of the original ketone (Harper, *loc. cit.*). This derivative occasionally exhibits dimorphism, having then m. p. *ca.* 160°.

*Reaction of 3-Methyl-2-*n*-pent-4'-enyl*cyclo*pent-2-en-1-one with* N-*Bromosuccinimide.*—The ketone (1·64 g.) (regenerated from the semicarbazone; b. p. 127—129°/20 mm., n_D^{20} 1·4948) reacted with *N*-bromosuccinimide (1·78 g., 1·0 mol.) in warm carbon tetrachloride (10 ml.). Refluxing was continued until the evolution of hydrogen bromide commenced. The suspension was then quickly cooled, filtered (0·91 g. of succinimide, 88%), and evaporated. Distillation of the residue gave, as the sole volatile product, unchanged ketone, b. p. 82—91°/0·35 mm., n_D^{20} 1·4997 (0·95 g.), and a polymeric residue. The distillate was converted into the semicarbazone (1·07 g., 48%), which had m. p. 172—173° after one crystallisation and did not depress the m. p. of the original ketone semicarbazone. The ketone reacted with 2 molecular proportions of *N*-bromosuccinimide but required the addition of benzoyl peroxide after 30 minutes' refluxing to complete the reaction.

In another experiment refluxing was continued until evolution of hydrogen bromide was complete. Without distillation the product was refluxed with silver acetate in glacial acetic acid. The suspension was filtered, the acetic acid removed in a vacuum, and the residue converted directly into the semicarbazone. The product had, however, m. p. 171—172° which was not depressed on admixture with the semicarbazone of the original ketone.

Addition of 10% bromine in carbon tetrachloride (1 mol.) to the ketone below 0° required illumination for decolorisation to occur. The 3-methyl-2-(4′ : 5′-dibromo-*n*-amyl)*cyclo*pent-2-en-1-one so formed was characterised by a 2 : 4-*dinitrophenylhydrazone*, m. p. 123—124° (Found: C, 41·3; H, 3·8. $C_{17}H_{20}O_4N_4Br_2$ requires C, 40·5; H, 4·0%). Without isolation the dibromo-ketone was treated with *N*-bromosuccinimide (1 mol.); reaction took place rapidly, with some evolution of hydrogen bromide towards the end. Refluxing of the tribromo-ketone with potassium iodide in ethanol effected only partial removal of the vicinal bromine atoms. This was confirmed by re-examination of the dibromo-ketone which likewise reacted only slightly with potassium iodide in ethanol.

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UNIVERSITY COLLEGE, SOUTHAMPTON.
KING'S COLLEGE (UNIVERSITY OF LONDON), STRAND, W.C.2. [*Received, January 3rd,* 1950.]

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201. *Some Compounds related to the Aromatic "Nitrogen Mustards."*

By GEORGE A. R. KON and JOHN J. ROBERTS.

The preparation of certain compounds related to the cytotoxic "nitrogen mustards" is described.

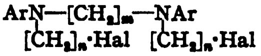
NUMEROUS di(halogenoalkyl)arylamines, of which di-(2-chloroethyl)aniline $Ph{\cdot}N(CH_2{\cdot}CH_2Cl)_2$ is typical, have been found to have a powerful cytotoxic activity and to inhibit the growth of transplanted tumours in rats (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824). A number of such compounds has been described (Ross, *J.*, 1949, 183; Everett and Ross, *ibid.*, p. 1972) and certain generalisations have been made in relating the structure of the compounds to their biological activity. Thus, it appears essential that two halogenoalkyl chains should be present and that the halogen atoms should not be separated from the nitrogen by more than two carbon atoms; the activity of these compounds could be satisfactorily related to the ease of hydrolysis of the halogen atoms in aqueous acetone.

It appeared of interest to test these conclusions by examining related compounds possessing two side chains of unequal length, and also compounds with side chains longer than the optimum but with additional substituents conferring the requisite reactivity on the halogen atoms.

For this purpose a series of anilino-alcohols was prepared. These call for little comment, except that 4-anilinobutanol, which had already been obtained (Ross and Everett, *loc. cit.*), has now been prepared more easily in a pure state by condensing aniline with 4-chlorobutyl acetate to give the crystalline 4-*anilinobutyl acetate*, which was then hydrolysed. The latter acetate could also be condensed with a second molecule of chlorobutyl acetate to give *di*-(4-*acetoxybutyl*)-*aniline*, and the parent compound was obtained in a pure state by alkaline hydrolysis; however, all attempts to prepare the corresponding chloro-derivative failed.

Condensation of the anilino-alcohols with ethylene chlorohydrin afforded compounds of the type $Ph{\cdot}N(CH_2{\cdot}CH_2{\cdot}OH){\cdot}[CH_2]_n{\cdot}OH$, where *n* was 2, 3, 4, and 5, and the products were then converted into the chlorides. Attempts to prepare the same compounds with the aid of ethylene oxide were not successful. Similar compounds were obtained when using 3-chloropropyl alcohol in place of ethylene chlorohydrin, but the series was not extended further because compounds with longer side chains were invariably inactive, in agreement with their low rate of hydrolysis in aqueous acetone.

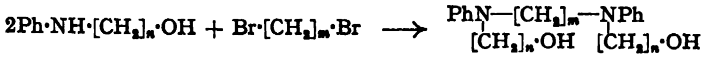
This inactivity was not due purely to steric factors such as the separation of the reacting groups in space owing to lengthening of the side chain; this was strikingly borne out by an examination of a series of compounds of the general type (I), in which the terminal halogen atoms can be more widely separated, for reactivity depends on their position with reference to the activating group, namely nitrogen.



$$\begin{array}{l}\mathrm{ArN{-}[CH_2]_m{-}NAr}\\ \mathrm{[CH_2]_n{\cdot}Hal\quad[CH_2]_n{\cdot}Hal}\end{array}$$

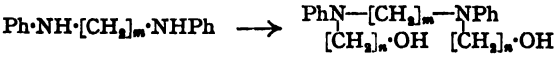
(I.)

For the preparation of compounds in which the nitrogen atoms are separated by two or more carbon atoms two methods are available and both have been used : in one of these two molecules of the anilino-alcohol are condensed with one of the appropriate alkylene dibromide, a method already much used by von Braun in analogous cases (*Ber.*, 1908, **41**, 2156) :



$$\mathrm{2Ph{\cdot}NH{\cdot}[CH_2]_n{\cdot}OH + Br{\cdot}[CH_2]_m{\cdot}Br} \longrightarrow \begin{array}{l}\mathrm{PhN{-}[CH_2]_m{-}NPh}\\ \mathrm{[CH_2]_n{\cdot}OH\quad[CH_2]_n{\cdot}OH}\end{array}$$

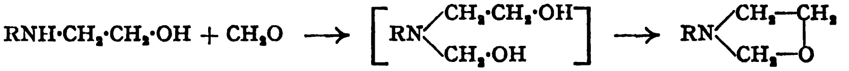
alternatively, an αω-dianilinoalkane is condensed with ethylene oxide or a chlorohydrin :



$$\mathrm{Ph{\cdot}NH{\cdot}[CH_2]_m{\cdot}NHPh} \longrightarrow \begin{array}{l}\mathrm{PhN{-}[CH_2]_m{-}NPh}\\ \mathrm{[CH_2]_n{\cdot}OH\quad[CH_2]_n{\cdot}OH}\end{array}$$

Chlorination of the hydroxyl groups then affords the appropriate chloro-compound. The second method appeared to be especially promising as a route to compounds in which $m = 1$, since Eibner has described the preparation of di-(*o*-tolyl)methane and other similar compounds (*Annalen*, 1898, **302**, 349). This compound was condensed with ethylene chlorohydrin to give a product which appeared to be mainly the desired dihydroxyethyl derivative, but it could not be completely purified and gave no definite compound on chlorination.

It was hoped to obtain similar compounds by a variant of the first method, namely by condensing anilino-alcohols with formaldehyde. The condensation of some ethanolamines with formaldehyde, acetaldehyde, and benzaldehyde has been studied by Knorr and Matthes (*Ber.*, 1901, **34**, 3484), who showed that the intermediate compounds lose water and cyclise to oxazolidines :



Bergmann, Ulpts, and Camacho (*ibid.*, 1922, **55**, 2796) found that phenetidinoethanol behaved similarly. We have prepared a number of *N*-aryloxazolidines in the same way. 3-Anilinopropanol also condensed readily with formaldehyde to afford 3-*phenyl*-1 : 3-*oxazine*. 4-Anilinobutanol gave under similar conditions what appeared to be the intermediate hydroxymethyl compound, which was unstable and lost water on distillation to pass into the cyclic compound, 3-*phenyl*-1 : 3-*pentoxazoline* (3-*phenyl*-1-*oxa*-3-*aza*cyclo*heptane*). 5-*Anilinopentanol* and 6-*anilinohexanol* appeared to react with formaldehyde, but on distillation the products decomposed and the starting materials were the only products isolated. All efforts to condense esters of anilino-alcohols with formaldehyde and so avoid cyclisation were fruitless.

The preparation of compounds in which the nitrogen atoms are more widely separated did not present much difficulty; the compounds of type (I) in which $n = m = 2$ were some of the most active compounds yet tested and this has prompted the preparation of several analogues, in which the group Ar and the side-chain were varied. It may be noted that aliphatic analogues of these, such as *NN'*-diethyl-*NN'*-di-(2-chloroethyl)ethylenediamine, have proved to be active cytotoxic agents (SK 882, Abstract of Final Report to the Chemical Corps, March 14th, 1948).

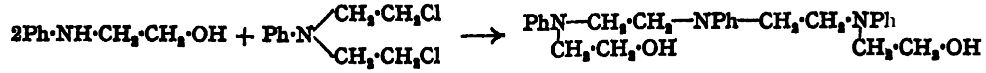
Biological activity is maintained in derivatives of propylenediamine and gradually falls off as the distance between the nitrogen atoms is increased. Lengthening of the halogenoalkyl side chains, on the other hand, leads to complete loss of activity, in agreement with the theoretical views developed above. Thus, already the di-3-chloropropyl derivative of *NN'*-diphenylethylenediamine is inactive.

To afford a comparison with the compounds already described by Ross (*loc. cit.*) a few representative compounds of type (I) have been hydrolysed in boiling 50% acetone–water for ½ hour and the following values obtained :

Ar.	*m*.	*n*.	% Hydrolysed.	Ar.	*m*.	*n*.	% Hydrolysed.
Ph	2	2	33	1-$C_{10}H_7$	2	2	67
Ph	3	2	40	2-$C_{10}H_7$	2	2	18
Ph	4	2	45	*p*-OMe·C_6H_4	2	2	55
Ph	5	2	44	Ph	2	3	<1
Ph	6	2	54	Ph	2	*	83

* Side chain = $\cdot CH_2\cdot CHMeCl$.

Interesting analogues of these compounds should be formed by the condensation of 2 moles of anilinoethanol with one of a di(halogenoalkyl)aniline:



$$2Ph{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH + Ph{\cdot}N\begin{smallmatrix}CH_2{\cdot}CH_2Cl\\CH_2{\cdot}CH_2Cl\end{smallmatrix} \longrightarrow \underset{CH_2{\cdot}CH_2{\cdot}OH}{PhN}{-}CH_2{\cdot}CH_2{-}NPh{-}CH_2{\cdot}CH_2{\cdot}\underset{CH_2{\cdot}CH_2{\cdot}OH}{NPh}$$

Unfortunately all attempts to prepare such compounds led to diarylpiperazines (cf. Davis and Ross, *J.*, 1949, 2831).

EXPERIMENTAL.

(M. p.s are uncorrected.)

Arylamino-alcohols.—2-Anilinoethanol was prepared as described by Schorygin and Smirnov (*J. Gen. Chem. Russia*, 1934, **4**, 830). 3-Anilinopropanol, which had previously been obtained in 29% yield by condensing allyl alcohol with aniline (Hromatka, *Ber.*, 1942, **75**, 379), has now been obtained in 70% yield from trimethylene chlorohydrin and aniline by Schorygin and Smirnov's procedure, namely by dropping the chlorohydrin (1 mol.) during ½ hour into aniline (2 mols.) and water (1 mol.) kept at about 140° and then gently boiling the mixture for 1 hour; alkali was added to the cooled product and the anilino-alcohol extracted with ether and purified by distillation. 2-Anilinopropanol (Dains, Joss, and Stubbs, *Univ. Kansas Sci. Bull.*, 1931, **20**, 161) was conveniently prepared by heating equimolecular quantities of aniline and propylene oxide to 150° for 15 hours and then working up the product as above (yield 70%). 4-Chlorobutyl acetate (Cloke and Pilgrim, *J. Amer. Chem. Soc.*, 1939, **61**, 2667) (0·1 mol.) was boiled under reflux with aniline (0·1 mol.), calcium carbonate (0·05 mol.), and water (50 c.c.) for 10 hours, with vigorous stirring; the product, isolated by means of ether, gave on distillation 25% of a fraction, b. p. 150—155°/1·8 mm., which solidified and then crystallised from pentane in plates, m. p. 33—34°, consisting of *4-anilinobutyl acetate* (Found: C, 69·8; H, 8·7. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·5%). The alcohol was obtained from the acetate by hydrolysis with cold methanolic potassium hydroxide and boiled at 138—140°/1 mm. (Found: C, 72·5; H, 9·2. Calc. for $C_{10}H_{15}ON$: C, 72·7; H, 9·2%). Pentamethylene chlorohydrin (Bennett and Heathcote, *J.*, 1929, 268) was boiled with 2 moles of aniline for 6 hours; excess of aqueous potassium hydroxide was added to the cooled product, which was extracted with ether, giving 45% of *5-anilinopentanol*, b. p. 164°/1·4 mm. (Found: C, 73·7; H, 9·7. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6%). Hexamethylene chlorohydrin (Müller and Vanc, *Monatsh.*, 1947, **77**, 259) gave on similar treatment a 74% yield of *6-anilinohexanol*, b. p. 138°/0·05 mm., crystallising as stout needles, m. p. 42°, from benzene–light petroleum (Found: C, 74·5; H, 10·0. $C_{12}H_{19}ON$ requires C, 74·5; H, 9·9%). When 2-naphthylamine was heated with ethylene chlorohydrin with or without the addition of chalk and water, *2-naphthylaminoethanol* could not be isolated from the product; it was, however, formed together with the *NN*-bishydroxyethyl compound (Ross, *loc cit.*) on heating naphthylamine with one mole of ethylene oxide to 100° for 6 hours; the crude reaction product was freed from unchanged naphthylamine and some dinaphthylamine by chromatography in benzene solution on Spence type H alumina; the hydroxylated compounds were recovered by stripping the column with methanol; they were treated with formaldehyde (see below), and the *oxazolidine* formed was separated by chromatography in ethereal solution and recovered from the first runnings; it formed plates, m. p. 91—92°, from methanol (Found: C, 78·3; H, 6·6. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%). The oxazolidine (5 g.) was dissolved in the minimum amount of alcohol, and 10 c.c. of hydrochloric acid were added, causing a deep red colour to develop. The solution was heated to the b. p., rapidly cooled, diluted, basified, and extracted with ether. The ethereal extract gave a good yield of 2-naphthylaminoethanol, b. p. ~180°/0·7 mm., m. p. 49—50° (crystallised after being rubbed with light petroleum) (Found: C, 76·5; H, 7·0%. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0%). The compound rapidly darkens on exposure to light and air and is therefore difficult to crystallise although a small amount of prisms has been obtained by slow evaporation of a benzene–light petroleum solution.

N-2-*Hydroxyethyl*-N-3′-*hydroxypropylaniline*, obtained from 3-anilinopropanol and ethylene chlorohydrin in 75% yield as described for anilinobutyl acetate, had b. p. 180—190°/0·3 mm. (Found: C, 67·7; H, 8·8. $C_{11}H_{17}O_2N$ requires C, 67·7; H, 8·8%).

N-2-Chloroethyl-*N*-3′-chloropropylaniline was prepared from the preceding compound by the general method given by Everett and Ross (*loc. cit.*) and was a pale yellow oil, which was analysed in the form of its *picrate*, yellow plates, m. p. 91° (Found: N, 12·7. $C_{17}H_{18}O_7N_4Cl_2$ requires N, 12·3%). The yield was 50%; the same method of chlorination was used throughout this work and gave yields varying from 40 to 60%.

N-2-*Hydroxyethyl*-N-4′-*hydroxybutylaniline*, obtained from anilinobutanol in 76% yield as described for the previous compound, had b. p. 180—190°/0·4 mm. (Found: C, 69·1; H, 9·5. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·2%).

N-2-Chloroethyl-*N*-4′-chlorobutylaniline was an oil which was analysed in the form of its *picrate*, yellow plates, m. p. 103—104° (Found: C, 45·9; H, 4·5. $C_{18}H_{20}O_7N_4Cl_2$ requires C, 45·5; H, 4·2%). When kept, the chloro-compound gradually deposited a solid, m. p. 174°. Titration with silver nitrate and dichlorofluorescein suggested that one chlorine had become ionic and the compound was probably *N*-phenyl-*N*-2-chloroethylpyrrolidinium chloride.

NN-*Di*-(*4-hydroxybutyl*)*aniline*. Equimolecular quantities of 4-anilinobutyl acetate and 4-chlorobutyl acetate were condensed as described under the preparation of the former compound (20 hours). The fraction, b. p. 190—210°/0·5 mm. (20% yield), was the *diacetate* (Found: C, 67·2; H, 8·3. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5%) from which the required alcohol was obtained on hydrolysis with cold methanolic potassium hydroxide; the *diol* had b. p. 190°/0·3 mm. (Found C, 70·7; H, 9·7. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·8%). All attempts to prepare a dichloro-compound were unsuccessful.

Oxazolidines.—The appropriate anilino-alcohol (5 g.) was rubbed with excess of 40% formaldehyde solution, whereupon (in most cases) a clear solution formed in 1—2 minutes. This then became cloudy and a heavy colourless oil (or solid) separated, which could be isolated by extraction with ether and purified by distillation or crystallisation; the yields were quantitative. The following were obtained:

Compound.	M. p. or b. p. (solvent).	Found, C, %.	Found, H, %.	Formula.	Required, C, %.	Required, H,
3-*Phenyloxazolidine*	B. p. 94°/1·5 mm., m. p. 28° (pentane)	70·8	7·3	$C_9H_{11}ON$	70·6	7·3
3-p-*Methoxyphenyloxazolidine*	Plates, m. p. 88° (light petroleum)	67·0	7·5	$C_{10}H_{13}O_2N$	67·0	7·5
3-*Phenyl-5-methyloxazolidine* *	B. p. 120°/6 mm., m. p. 37—38° (pentane)	73·2	8·0	$C_{10}H_{13}ON$	73·6	8·0
3-*Phenyl*-1 : 3-*oxazine* *	B. p. 94°/0·4 mm.	73·7	7·8	$C_{10}H_{13}ON$	73·6	8·0
3-*Phenylpentoxazolidine* (3-*phenyl*-1-*oxa*-3-*aza*cyclo*heptane*)	B. p. 115°/0·4 mm.	74·6	8·7	$C_{11}H_{15}ON$	74·7	8·7
2 : 3-*Diphenyloxazolidine* †	Needles, m. p. 84—85° (methanol)	80·0	7·1	$C_{15}H_{15}ON$	80·0	6·7

* Purified by chromatography. † Benzaldehyde used in place of formaldehyde.

Diamines.—NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*ethylenediamine.* 2-Anilinoethanol (0·2 mol.), ethylene dibromide (0·1 mol.), chalk (0·15 mol.), and water (100 c.c.) were boiled under reflux with mechanical stirring for 10 hours. The product was extracted with benzene, evaporated, and distilled; the fraction, b. p. 220—230°/0·7 mm., obtained in 74% yield, solidified and crystallised from benzene–light petroleum (b. p. 60—80°) in plates, m. p. 89—90° (Found: C, 72·2; H, 8·0. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·1%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*ethylenediamine* formed stout needles, m. p. 81—82°, from light petroleum (b. p. 40—60°) (Found: C, 64·0; H, 6·5. $C_{18}H_{22}N_2Cl_2$ requires C, 64·1; H, 6·6%).

The following compounds were prepared by exactly similar methods unless otherwise stated:

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*trimethylenediamine*, b. p. 210—222°/0·6 mm., flattened needles (from benzene–light petroleum), m. p. 112—113° (75%) (Found: C, 72·8; H, 8·6. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·3%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*trimethylenediamine*, an oil (Found: C, 65·1; H, 7·1. $C_{19}H_{24}N_2Cl_2$ requires C, 64·9; H, 6·9%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*tetramethylenediamine*. In the preparation of this compound and its pentamethylene analogue no chalk or water was used, the components being heated on the steam-bath for 6 hours, and the cooled mixture then treated with an excess of 2N-sodium hydroxide. The fraction, b. p. 200—220°/0·5 mm. (18% yield), solidified and was rubbed with ether, and then crystallised from benzene–light petroleum, forming plates, m. p. 79—80° (Found: C, 73·3; H, 8·5. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·6%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*tetramethylenediamine* crystallised from pentane in prisms, m. p. 65° (Found: C, 65·4; H, 7·0. $C_{20}H_{26}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*pentamethylenediamine* was obtained exactly like the tetramethylene compound (yield 22%); the crude fraction, b. p. 200—210°/0·4 mm., was analysed (Found: C, 72·6; H, 8·6. $C_{21}H_{30}O_2N_2$ requires C, 73·7; H, 8·8%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*pentamethylenediamine* was a colourless oil, b. p. 170°/0·2 mm. (Found: C, 66·4; H, 7·6. $C_{21}H_{28}N_2Cl_2$ requires C, 66·5; H, 7·4%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxyethyl*)*hexamethylenediamine*, obtained in 66% yield from *NN*′-diphenylhexamethylenediamine (von Braun, *Ber.*, 1910, **43**, 2859) and ethylene chlorohydrin by the chalk and water process, had b. p. 280°/2 mm. (Found: C, 74·0; H, 9·1. $C_{22}H_{32}O_2N_2$ requires C, 74·1; H, 9·1%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloroethyl*)*hexamethylenediamine* was crystallised successively from light petroleum (b. p. 40—60°), alcohol, and again light petroleum, forming prisms, m. p. 66° (Found: C, 67·1; H, 8·0. $C_{22}H_{30}N_2Cl_2$ requires C, 67·2; H, 7·7%).

NN′-*Diphenyl*-NN′-*di*-(2-*hydroxypropyl*)*ethylenediamine* was produced in 61% yield from 2-anilinopropanol and ethylene dibromide. It was also formed on heating *NN*′-diphenylethylenediamine with an excess of propylene oxide in a sealed tube to 160° for 15 hours and was an oil, b. p. ~220°/0·1 mm. (Found: C, 73·2; H, 8·6. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·6%). In the latter preparation there was formed a by-product boiling some 10° lower and forming plates (from methanol), m. p. 166—167°, probably 2-*ethyl*-1 : 3-*diphenyltetrahydroglyoxaline* (Found: C, 80·5; H, 8·3. $C_{17}H_{20}N_2$ requires C, 80·9; H, 8·0%). The formation of this compound presupposes the rearrangement of propylene oxide to propaldehyde which is known to occur at high temperature (Ipatiew and Leontowitsch, *Ber.*, 1903, **36**, 2017). When the reaction with propylene oxide was interrupted after 10 hours, the product was a solid, prisms (from benzene–light petroleum), m. p. 92°, consisting of NN′-*diphenyl*-N-(2-*hydroxypropyl*)-*ethylenediamine* (Found: C, 75·4; H, 8·0. $C_{17}H_{22}ON_2$ requires C, 75·5; H, 8·2%). The *picrate* had m. p. 142° (Found: N, 14·4. $C_{23}H_{25}O_8N_5$ requires N, 14·0%).

NN′-*Diphenyl*-NN′-*di*-(2-*chloropropyl*)*ethylenediamine* was an oil (Found: C, 65·5; H, 7·3. $C_{20}H_{26}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN′-*Diphenyl*-NN′-*di*-(3-*hydroxypropyl*)*ethylenediamine* (66% yield from 3-anilinopropanol) had m. p. 75° after crystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 72·9; H, 8·8. $C_{20}H_{28}O_2N_2$ requires C, 73·2; H, 8·6%).

NN′-*Diphenyl*-NN′-*di*-(3-*chloropropyl*)*ethylenediamine* formed small prisms, m. p. 53·5—54°, after two crystallisations from pentane (Found: C, 66·1; H, 7·2. $C_{20}H_{26}N_2Cl_2$ requires C, 65·7; H, 7·2%).

NN′-*Diphenyl*-NN′-*di*-(4-*hydroxybutyl*)*ethylenediamine* (54% yield from 4-anilinobutanol) boiled at 220—240°/0·5 mm. and formed needles, m. p. 81°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 74·1; H, 9·1. $C_{22}H_{32}O_2N_2$ requires C, 74·1; H, 9·1%).

NN′-*Diphenyl*-NN′-*di*-(*4-chlorobutyl*)*ethylenediamine* formed plates, m. p. 61°, from pentane (Found: C, 67·2; H, 8·1. $C_{22}H_{30}N_2Cl_2$ requires C, 67·2; H, 7·7%).

NN′-*Di*-(p-*methoxyphenyl*)-NN′-*di*-(*2-hydroxyethyl*)*ethylenediamine*, obtained in 62% yield from *N*-(2-hydroxyethyl)-*p*-anisidine (Ross, *J*., 1949, 183), crystallised from benzene–light petroleum (b. p. 60—80°) in fine needles, m. p. 92—93° (Found: C, 66·2; H, 8·2. $C_{20}H_{28}O_4N_2$ requires C, 66·6; H, 7·8%).

NN′-*Di*-(p-*methoxyphenyl*)-NN′-*di*-(*2-chloroethyl*)*ethylenediamine* formed lustrous plates, m. p. 63—64° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 60·6; H, 6·4. $C_{20}H_{26}O_2N_2Cl_2$ requires C, 60·5; H, 6·6%).

NN′-*Di-2-naphthyl*-NN′-*di*-(*2-hydroxyethyl*)*ethylenediamine*. *NN′*-Di-2-naphthylethylenediamine (Bischoff and Hausdorfer, *Ber*., 1890, **23**, 1985) (15 g.) was heated in a sealed tube with 5·5 c.c. of ethylene oxide and 5 c.c. of benzene for 12 hours at 160°. The residue obtained after evaporation of the solvent solidified and crystallised from benzene–light petroleum (b. p. 60—80°) in pearly plates, m. p. 96—97° (80%) (Found: C, 78·0; H, 7·1. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1%).

NN′-*Di-2-naphthyl*-NN′-*di*-(*2-chloroethyl*)*ethylenediamine* crystallised from benzene–light petroleum (b. p. 40—60°) in plates, m. p. 124—125° (Found: C, 71·5; H, 6·1. $C_{26}H_{26}N_2Cl_2$ requires C, 71·5; H, 6·0%).

NN′-*Di-1-naphthyl*-NN′-*di*-(*2-hydroxyethyl*)*ethylenediamine*, obtained in the same way as the 2-naphthyl derivative, formed plates, m. p. 92—93°, from benzene–light petroleum (Found: C, 78·1; H, 7·2. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1%). The *dipicrate* had m. p. 125° (Found: C, 53·3; H, 3·9. $C_{38}H_{34}O_{16}N_8$ requires C, 53·1; H, 4·0%).

NN′-*Di-1-naphthyl*-NN′-*di*-(*2-chloroethyl*)*ethylenediamine* crystallised from light petroleum (b. p. 60—80°) in stout prisms, m. p. 111° (Found: C, 71·6; H, 6·2. $C_{26}H_{26}N_2Cl_2$ requires C, 71·5; H, 6·0%).

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THE CHESTER BEATTY RESEARCH INSTITUTE,
THE ROYAL CANCER HOSPITAL, FULHAM ROAD,
LONDON, S.W.3.

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202. *The Nitration of Polystyrene.*

By H. ZENFTMAN.

Polystyrene has been nitrated with mixtures of nitric and sulphuric acids. By regulating the conditions of nitration, products with degrees of substitution between 1·0 and 2·0 (nitrogen content, 9·4—14·4%) could be obtained, but attempts to obtain higher substitution were unsuccessful. Oxidative fission of nitropolystyrenes produced *p*-nitrobenzoic and 2 : 4-dinitrobenzoic acids. During nitration some degradation of the original polystyrene chain took place, but could be controlled under suitable conditions. The properties of various nitropolystyrenes have been determined.

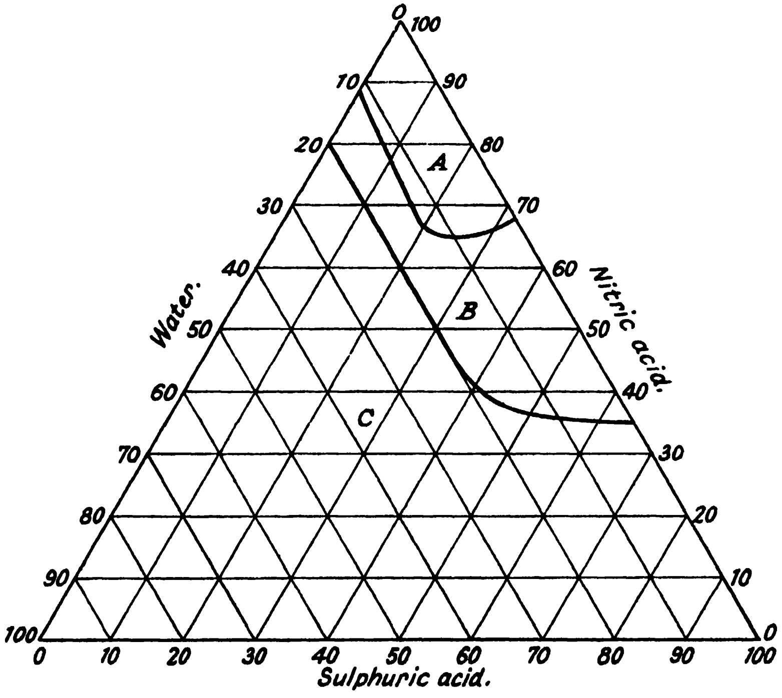
IN the first recorded nitration of polystyrene Blyth and Hofmann (*Annalen*, 1845, **53**, 316) boiled a glassy polymer of styrene with fuming nitric acid and obtained a product of 10·6% nitrogen content which they called "nitrometastyrol." This product was soluble in nitric acid and sulphuric acid, but insoluble in most other solvents. Elementary analysis of this product led these authors to incorrect formulations for styrene and nitrostyrene. Bachman *et al.* (*J. Org. Chem.*, 1947, **12**, 108) nitrated polystyrene with fuming nitric acid in a similar way at 50° and 150° and obtained products with 10·0 and 11·22% of nitrogen, respectively. They were unable to obtain dinitropolystyrene. Recent knowledge of high polymers suggested that a range of nitropolystyrenes differing in chain length and degree of nitration, and consequently in solubility and solution viscosity, should be accessible by suitable choice of starting material and nitration conditions.

Preliminary experiments showed that nitration of polystyrene in a non-solvent medium merely gave a negligible surface reaction. When the nitrating medium caused swelling of the granules the nitration was more pronounced, but the product was not uniform and unchanged polymer still persisted. It was, therefore, essential to use a nitrating medium capable of completely dissolving the polystyrene. Mixtures of nitric and sulphuric acids were found to be the most suitable nitrating agents for this work. Investigation of the solubility of polystyrene after two hours at 20° in variants of the system nitric acid–sulphuric acid–water gave the results summarised in the triangular diagram.

Area *A* included all nitrating media of practical importance, and the curved boundary of area *C* indicated the approximate minimum degree of dilution required to precipitate the product. Table II summarises the effects of times from 1 to 24 hours and temperatures from 10° to 50° on using various nitrating acids having compositions lying within area *A*.

It was found that polystyrene was nitrated by every nitric or nitric–sulphuric acid composition capable of dissolving it. The lowest nitrogen content of nitropolystyrene obtained from clear solutions was approximately 9·4%, corresponding to one nitro-group per styrene unit, whereas the highest nitrogen content obtained was 14·4%, corresponding to two nitro-groups per styrene unit. Any intermediate substitution could be obtained by controlling the composition of the nitrating acid, the temperature, and the time of nitration. The molecular weight of the initial polystyrene (as indicated by the viscosity data in Table IV) was found to have little influence on the nitrogen content of the final product. The introduction of the first nitro-group was rapid and appeared to accompany the dissolution of the polystyrene. The rate of mononitration could be regulated by modifying the rate of dissolution of polystyrene in the nitrating acid, *e.g.*, by variation of the particle size. Introduction of the second group took place at a slower rate which was dependent on the dilution of the nitrating acid and the temperature of nitration. Addition of polystyrene to nitrating acid was always accompanied by evolution of heat, and efficient stirring and cooling were necessary to control the nitration. It was observed, however, during renitration of nitropolystyrene (9·8% nitrogen content) to a higher nitrogen content (14·1%) that it dissolved in the nitric–sulphuric acid quickly but without significant evolution of heat. For each nitrating acid composition and temperature of nitration there was a limiting degree of substitution which, as a rule, was attained more rapidly the higher the temperature. Attempts were made to obtain nitropolystyrene of a higher degree of substitution than 2·0 by carrying out nitration in sealed tubes at high temperatures (120° and 150°), but these met with no success. The nitrogen contents of the products were determined by the Dumas method. Elementary analyses of a few samples of nitropolystyrene of various nitrogen contents were consistent with the expected empirical formula $C_8H_{8-n}(NO_2)_n$, where n represents the degree of substitution calculated from the equation $n = 104N/(1400 - 45N)$ (where $N = \%$ of nitrogen).

Solubility of polystyrene in nitric acid–sulphuric acid–water mixtures.



Area A. Solubility. Area B. Gelatinisation. Area C. Insolubility.

The positions of the nitro-groups in the polymeric chain were determined by oxidative fission of nitropolystyrenes. Aromatic nitro-compounds with an aliphatic side chain are readily oxidised to the corresponding nitrobenzoic acids. Bigelow (*J. Amer. Chem. Soc.*, 1919, **41**, 1575) obtained good yields of mononitrobenzoic acids from mononitrotoluenes by using potassium permanganate in alkaline solutions. For the same purpose Feldman *et al.* (*J. Gen. Chem. Russia*, 1945, **15**, 962) used manganese dioxide and concentrated sulphuric acid. Dinitrotoluenes were oxidised to dinitrobenzoic acids by Sirks (*Rec. Trav. chim.*, 1908, **27**, 221), using nitric acid or potassium permanganate, and by Buehler and Calfee (*Anal. Chem.*, 1934, **6**, 351), using chromic acid.

Oxidation of nitropolystyrenes to nitrobenzoic acids was found to be difficult, and all methods gave large amounts of unchanged nitropolystyrene. The best results were obtained by using manganese dioxide in concentrated sulphuric acid. Only *p*-nitrobenzoic and 2 : 4-dinitrobenzoic acids could be isolated. Nitropolystyrene of a nitrogen content 9·4% (degree of substitution 1·0) gave on oxidation only *p*-nitrobenzoic acid, but nitropolystyrenes with a degree of substitution between 1 and 2 always gave both *p*-nitrobenzoic and 2 : 4-dinitrobenzoic acids. All attempts to isolate mononitrobenzoic acids from the oxidation of a nitropolystyrene of a degree of substitution approximately 2·0 were unsuccessful, and this suggested the absence of nitro-groups in the aliphatic chain.

These results indicated that during nitration of polystyrene only nuclear substitution occurred, a maximum of two nitro-groups entering each benzene ring. The first group entered the *p*-position, the second being randomly distributed along the polymer chain entirely or predominantly in the *o*-position. It was not possible, however, to state definitely that substitution was entirely limited to the *o*- and the *p*-positions on account of the low yields of nitrobenzoic acids calculated on unrecovered nitropolystyrene (usually less than 40%).

Degradation of the chain length of the polystyrene during nitration was estimated approximately by measuring the viscosities of the nitrated products and the original polystyrene. Viscosities were measured in dilute *cyclo*hexanone solutions at such concentration that $\eta_{\text{rel.}}$ had values between 1·1 and 1·2, and were applied to the following approximation of Staudinger's expression: Degree of polymerisation $= k(\eta_{\text{rel.}} - 1)/C$; k for nitropolystyrene was unknown, but may be taken as constant in the range of nitrogen contents under consideration.

It is, moreover, considered unlikely that k for polystyrene will be halved when the material is nitrated, so that the results in Table III indicate that under all conditions of nitration some degradation of the polymer chain occurred. However, by carrying out the nitration under strict conditions of temperature and time, it could to a large extent be controlled. Degradation was most rapid during the first stages of nitration and then continued more slowly. High nitration temperatures favoured degradation., Table IV also shows that the decrease in degree of polymerisation of polystyrene with higher initial molecular weight was relatively greater.

Nitropolystyrenes of 9·4% to 14·4% nitrogen content were amorphous, pale cream-coloured to light yellow solids which darkened on exposure to daylight. When heated to 300°, nitropolystyrenes decomposed without melting, at a rate increasing with nitrogen content, and evolved greyish-yellow gases leaving a black residue. Nitropolystyrenes were soluble in a restricted range of solvents to form viscous solutions.

Solubility increased with nitrogen content (Table I). In some solvents nitropolystyrene underwent limited swelling, forming gels.

TABLE I.

Solubility of nitropolystyrenes of different nitrogen contents in various solvents at 20°.

	Nitrogen content of nitropolystyrene, %.						
Solvent.	9·8.	11·7.	12·4.	13·0.	13·4.	13·8.	14·4.
Nitric acid, 90%	S	S	S	S	S	S	S
Ethylene dinitrate	S	S	S	S	S	S	S
Nitroglycerol	S	S	S	S	S	S	S
Furfuraldehyde	G	S	S	S	S	S	S
*cyclo*Pentanone	SW	S	S	S	S	S	S
*cyclo*Hexanone	SW	G	*S*	*S*	*S*	*S*	*S*
Dinitrotoluene (liquid mixture)	*G*	*S*	*S*	*S*	*S*	*S*	*S*
Mononitrotoluene (mixture)	SW	*G*	*G*	*S*	*S*	*S*	*S*
Nitrobenzene	G	*S*	*S*	*S*	*S*	*S*	*S*
Nitromethane	SW	G	G	G	G	G	G
Acetone	I	I	I	I	SW	SW	SW

S = soluble at 20°. *S* = requires heating to facilitate dissolution, remains in solution when cooled to 20°. G = gelatinised. *G* = gelatinised when heated. SW = swelling observed. I = no visible reaction.

EXPERIMENTAL.

Nitration of Polystyrene.—Nitration was carried out by adding granular polystyrene to a 10—20-fold weight of nitrating acid with vigorous stirring. The initial temperature of the acid was about −10°, and the whole of the polystyrene was added within 2—3 minutes. The temperature increased immediately after addition of polystyrene but effective cooling prevented it from exceeding 20°. After approximately

30 minutes the temperature was kept steady at the desired point, and maintained there by either cooling or heating. The viscosity of the mixture increased and the rate of stirring was reduced. Rapid addition of polystyrene to acid at low temperature was a necessary condition for obtaining a product with consistent properties. If the addition was carried out slowly at a constant temperature the rise of viscosity hindered the immersion and dispersion of further portions of polystyrene and caused local overheating of the particles. This was indicated by the appearance of brown fumes, and also by an excessively degraded product. When the nitration was finished, the mixture formed a clear, straw-coloured or brown, viscous liquid. Nitropolystyrene was precipitated from the solution by running the liquid in one or many very thin streams into gently stirred cold water. The precipitated product formed coils of threads which gradually became brittle and finally broke up into easily handled elongated granules which were sufficiently porous to permit washing out of the last traces of acid. When mechanical losses were avoided the weight of product as a percentage of the weight of initial polystyrene, approximated to the theoretical value of $100 + 100N/(31{\cdot}11 - N)$ % (N = % of nitrogen).

A typical nitration was carried out as follows: Mixed acid (300 ml.; composition: HNO_3, 73·2; H_2SO_4, 26·3; HNO_2, 0·1; H_2O, 0·4%) was cooled to −10° in a wide-necked conical flask. Polystyrene (125 g.; *M*, 210,000; particle size, 16—30 B.S. gauge) was added during two minutes, the temperature rising to 18°. Cooling with ice-salt and effective stirring during the first 30 minutes were required to prevent a further rise of temperature. After 30 minutes the temperature settled at 20°. After 1 hour from the start the whole of polystyrene had dissolved. Slow stirring was maintained for a further 3 hours at 20°, and the solution was then run from a dropping-funnel during 40 minutes into slowly stirred water (4—5 l.). The thread-like product was broken up into short lengths, washed five times by decantation, filtered off, washed on the filter, and steeped in water overnight. The filtered product was ground for 16 hours in a porcelain ball-mill with water (approx. 5 parts). Filtration, washing with water at 90—95° until the washings were neutral to methyl-orange, and drying to constant weight gave a product (42 g.) containing N, 13·4% (by Dumas's method). The degree of substitution was found to be 1·75, and ultimate analysis gave C, 51·9; H, 3·1% [Calc. for $C_8H_{6\cdot25}(NO_2)_{1\cdot75}$: C, 52·5; H, 3·4%].

TABLE II.

Influence of conditions of nitration on nitrogen content of nitropolystyrene.

Nitrating acid composition, %.				Temp. of nitration.	Time of nitration (hrs.).	Nitrogen content of nitropolystyrene (%).	Degree of substitution (*n*).
HNO_3.	H_2SO_4.	HNO_2.	H_2O.				
72·73	28·09	0·24	−1·06	10°	1	12·4	1·53
,,	,,	,,	,,	,,	2	12·8	1·62
,,	,,	,,	,,	,,	3	13·2	1·70
,,	,,	,,	,,	,,	5	13·3	1·73
,,	,,	,,	,,	,,	7	13·4	1·75
,,	,,	,,	,,	,,	24	13·4	1·75
,,	,,	,,	,,	20	1	12·8	1·62
,,	,,	,,	,,	,,	2	13·3	1·73
,,	,,	,,	,,	,,	3	13·4	1·75
,,	,,	,,	,,	,,	4	13·4	1·75
,,	,,	,,	,,	,,	5	13·6	1·80
,,	,,	,,	,,	30	1	13·1	1·68
,,	,,	,,	,,	,,	3	13·7	1·82
,,	,,	,,	,,	,,	4	14·1	1·92
,,	,,	,,	,,	,,	6	14·1	1·92
,,	,,	,,	,,	40	1	13·3	1·73
,,	,,	,,	,,	,,	2	13·8	1·84
,,	,,	,,	,,	,,	4	14·3	1·97
,,	,,	,,	,,	50	1	13·7	1·82
,,	,,	,,	,,	,,	2	14·2	1·94
,,	,,	,,	,,	,,	3	14·4	2·00
72·98	22·29	0·25	4·48	20	1	11·7	1·39
,,	,,	,,	,,	,,	3	12·0	1·45
,,	,,	,,	,,	,,	4	12·8	1·62
,,	,,	,,	,,	,,	5	13·1	1·68
,,	,,	,,	,,	,,	6	13·3	1·73
76·75	15·30	0·10	7·85	20	1	10·0	1·09
,,	,,	,,	,,	,,	3	11·6	1·37
,,	,,	,,	,,	,,	4	11·8	1·41
,,	,,	,,	,,	,,	6	12·1	1·47
66·40	20·30	0·10	13·20	20	2	9·5	1·02
,,	,,	,,	,,	,,	4	9·7	1·05
,,	,,	,,	,,	,,	6	9·8	1·06

Molecular weight of polystyrene used, 210,000. Ratio of acid to polystyrene, 20 : 1.

Oxidation of High-nitrogen Nitropolystyrene with Manganese Dioxide.—Finely ground nitropolystyrene (50 g.; N, 14·2%) was suspended in 96% (w/w) sulphuric acid (250 ml.) and left overnight. The liquid was heated in an oil-bath to 135°, and manganese dioxide (170 g.; MnO_2 content, 80%) was added during 16 hours in small portions at intervals of 15—20 minutes. The hot liquid was poured on crushed ice

(900 g.), and the product filtered, giving a solid residue (i) and a filtrate (ii). Residue (i) was washed with water (150 ml.), the washings being added to (ii), then suspended in water (200 ml.), made alkaline with concentrated sodium carbonate solution, heated to 85°, and filtered hot, giving a filtrate (iii) and a residue (iv). Residue (iv) was washed with hot water, separated by decantation from heavy particles of manganese dioxide, heated with diluted sulphuric acid, filtered, washed, and dried to constant weight to yield unconverted nitropolystyrene (30 g.). Filtrate (iii) was made acid (Congo-red paper) with the minimum amount of sulphuric acid (70% w/w), cooled, and filtered from traces of precipitate, giving filtrate (v).

TABLE III.

Influence of temperature and time of nitration on the viscosity of nitropolystyrene.

Nitration conditions.		Product.			
Temp.	Time (hrs.).	Nitrogen content (%).	C, g./100 ml.	$\eta_{rel.}$	$(\eta_{rel.}-1)/C$.
20°	2	13·2	0·165	1·148	0·90
,,	4	13·4	0·217	1·165	0·76
,,	5	13·6	0·200	1·142	0·71
30	1	13·1	0·220	1·151	0·69
,,	3	13·7	0·200	1·118	0·59
,,	4	14·1	0·204	1·107	0·52
40	1	13·3	0·200	1·106	0·53
,,	2	13·8	0·212	1·106	0·50
,,	4	14·3	0·224	1·108	0·48
50	1	13·7	0·306	1·119	0·39
,,	2	14·2	0·286	1·103	0·36
,,	3	14·4	0·323	1·120	0·34

The original polystyrene used in these nitrations had $(\eta_{rel.}-1)/C = 1{\cdot}87$ (determined in *cyclo*hexanone, $C = 0{\cdot}060$). Nitrating acid used: HNO_3, 72·7; H_2SO_4, 28·1; HNO_2, 0·2; H_2O, −1·0%.

TABLE IV.

Influence of viscosity of the polystyrene on the nitrogen content and the viscosity of nitropolystyrene.

Polystyrene.	Nitropolystyrene.		Polystyrene.	Nitropolystyrene.		Polystyrene.	Nitropolystyrene.	
$(\eta_{rel.}-1)/C$.	N, %.	$(\eta_{rel.}-1)/C$.	$(\eta_{rel.}-1)/C$.	N, %.	$(\eta_{rel.}-1)/C$.	$(\eta_{rel.}-1)/C$.	N, %.	$(\eta_{rel.}-1)/C$.
1·05	13·58 13·52	0·54	1·87	13·48 13·41	0·76	4·80	13·45 13·42	1·07

Composition of nitrating acid: HNO_3, 72·2; H_2SO_4, 26·4; HNO_2, 0·2; H_2O, 1·2%. Temperature, 20°; time, 4 hours.

Filtrate (v) gave a residue (vi; 1·1 g.) on extraction with ether (100 ml.) and evaporation of the extract. Residue (vi) was dissolved in the minimum amount of hot water, and decolorised with charcoal. Successive crops of crystals had m. p.s between 178° and 182°, which were not depressed on admixture with 2 : 4-dinitrobenzoic acid.

Filtrate (ii) was extracted with ether (150 ml.), 300 ml. of (ii) being used at a time, and the ether extract re-used. After evaporation, residue (vii) was obtained (7·7 g.). Residue (vii), crystallised from water (charcoal), gave crops of crystals with m. p.s between 177° and 181°, undepressed on admixture with 2 : 4-dinitrobenzoic acid.

Oxidation of Low-nitrogen Nitropolystyrene with Manganese Dioxide.—Nitropolystyrene (20 g.; N, 12·3%) was suspended in 75% (w/w) sulphuric acid (300 g.), and manganese dioxide (95 g.; MnO_2 content, 80%)was gradually added at 135° during 12 hours. The liquid was poured into water (350 ml.) and filtered when cold, giving a residue (i) and a filtrate (ii). Residue (i) was washed with water (50 ml.), the washings being added to (ii), and the residue suspended in water (120 ml.), made alkaline, and filtered hot, giving a filtrate (iii) and residue (iv). Residue (iv), washed with dilute sulphuric acid and water, dried, and analysed for nitrogen, was shown to contain nitropolystyrene (11·5 g.).

Ether-extraction of filtrate (ii) yielded 2 : 4-dinitrobenzoic acid (1·3 g.). Filtrate (iii) was made acid, left overnight in a cool place, and filtered to give a residue (v) and filtrate (vi). Residue (v) and the ethereal extract of filtrate (vi) gave crystals (total yield 1·5 g.) which on recrystallisation from water had m. p. 241° (undepressed by *p*-nitrobenzoic acid).

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IMPERIAL CHEMICAL INDUSTRIES LIMITED,
NOBEL DIVISION, STEVENSTON, AYRSHIRE.

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203. *The Electrical Conductivity of Iodine Monochloride and Iodine Trichloride.*

By N. N. Greenwood and H. J. Emeléus.

The electrical conductivity of molten iodine monochloride passes through a maximum at 40°. The conductivity of solid and liquid iodine trichloride has been measured in the range 70—150°. That of the solid increased rapidly with increasing temperature. There was no marked discontinuity at the melting point. In the molten state there was a maximum in the conductivity–temperature curve at 111°. It was shown that the maximum in the case of the monochloride was probably due to a decrease with rising temperature in the number of ions present. The degree of ionisation in molten iodine monochloride was of the order of 1%. For neither compound was there any indication of a decomposition potential. On prolonged electrolysis of molten iodine monochloride a small back e.m.f. was observed.

Both iodine monochloride and iodine trichloride dissolve in a variety of solvents and in many cases such solutions are found to conduct electricity. For instance, iodine monochloride is a conductor when dissolved in acetic acid, nitrobenzene, arsenic trichloride, sulphur dioxide, sulphuryl chloride, or water, and the trichloride conducts in all of these solvents, as well as in dichloroacetic acid and liquid bromine. Solutions of iodine trichloride in carbon tetrachloride, silicon tetrachloride, and chloroform are, however, non-conducting (Plotnikov and Rokotyan, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 723). Evidence for the nature of the ions in the molten iodine chlorides cannot readily be obtained directly but in the above solutions fairly definite deductions may be made. In the case of solutions of iodine monochloride dissociation into I^+ and $[ICl_2]^-$ appears most likely. This explains why electrolysis results in the deposition of iodine at both the cathode and the anode since, at the latter, a disproportionation of ICl_2 into I and ICl_3 (or I and Cl) could occur. This also explains why the concentration of both halogens (either free or in combined form) increases at the anode although the ratio of iodine to chlorine decreases (Sandonnini and Borgello, *Atti Accad. Lincei*, 1937, **25**, 46).

The nature of the ions formed by iodine trichloride in solution is less clear. Bruns (*Z. physikal. Chem.*, 1925, **118**, 89) claimed that, when an acetic acid solution was electrolysed, the whole of the iodine trichloride migrated to the anode. To explain this and also certain dilution effects the equilibrium $ICl_3,nCH_3\cdot CO_2H \rightleftharpoons ICl_3^{--} + (CH_3\cdot CO_2H)_n^{++}$ was postulated. Other equilbria which have been suggested are: $ICl_3 \rightleftharpoons I^{+++} + 3Cl^-$ and $ICl_3 \rightleftharpoons I^+ + Cl_3^-$. Yet another possibility, which is supported by the existence of salts such as $KICl_4$, is: $2ICl_3 \rightleftharpoons ICl_2^+ + ICl_4^-$. It is not certain that the ions in the molten compound will be identical with those in solution, but for the purposes of calculations of ion concentrations made later, the existence of I^+ and ICl_2^- in molten ICl has been assumed. The conductivity of molten iodine monochloride at 35° was measured by Cornog and Karges (*J. Amer. Chem. Soc.*, 1932, **54**, 1882), who showed that after repeated crystallisation the specific conductivity at this temperature was $4{\cdot}57$—$4{\cdot}59 \times 10^{-3}$ohm^{-1}cm.$^{-1}$. The compound was also shown to behave as an ionising solvent towards potassium chloride and ammonium chloride. Fialkov and Goldman (*J. Gen. Chem. Russia*, 1941, **11**, 910) found a conductivity of $4{\cdot}87$—$5{\cdot}39 \times 10^{-3}$ohm^{-1}cm.$^{-1}$ at 35° after purification by distillation at atmospheric pressure. During the course of the work described below, Fialkov and Shor (*Zhur. Obsch.*, 1948, **18**, 14) showed the existence of an extended maximum in the temperature–conductivity curve for molten iodine monochloride. The existence of this maximum was observed independently in the present work, though the absolute values of the conductivity of iodine monochloride were rather lower than those reported by Fialkov and Shor. No previous observations have been recorded on the conductivity of molten iodine trichloride, which also passes through a maximum. A discussion of these maxima and of the absence of a decomposition potential in either of the iodine chlorides is given later.

Experimental.

Iodine monochloride, prepared by Cornog and Karges's method (*loc. cit.*), was purified by recrystallisation in a static vacuum in an apparatus, shown in Fig. 1, in which a conductivity cell of the conventional type with sealed-in platinum electrodes was incorporated. About 100 g. of the monochloride were melted in the right-hand bulb, about 80% of the melt was allowed to crystallise, and the supernatant liquid was poured into the left-hand bulb. This process was repeated until the final batch of crystals showed the same m. p. on two successive operations. Usually four or five recrystallisations were found to give extremely pure iodine chloride having m. p. 27·20° as given by Cornog and Karges (*loc. cit.*). These pure crystals were then melted and poured into the cell, which was sealed at the constriction. Conductivities were measured by using the amplified output of a 1000-cycle oscillator in a Wheatstone-type network, and the balance point was detected electronically with a cathode-ray oscilloscope. The thermostat was controlled to ±0·05° by a contact thermometer in a large oil-bath.

The results obtained are shown in Fig. 2. Curve I shows data for impure iodine monochloride between the m. p. (27·2°) and 65°. Curve II represents the results for a purer sample : not only is the conductivity less, but there is a maximum at 45°. In Curve III and Table I the results for highly purified iodine monochloride are summarised. The conductivity is still lower and the maximum has been displaced to 40°. The data in Table I were reproducible, the value of 4·60 × 10^{-3}ohm^{-1}cm.$^{-1}$ for the conductivity at 35° being in close agreement with Cornog and Karges's value (*loc. cit.*). In col. 4 the values of a quantity μ/n are given. This function has been extensively used to compare the conductivities of molten chlorides at their melting points (Biltz and Klemm, *Z. anorg. Chem.*, 1926, 152, 267). The quantity n is defined to be one less than the number of ions formed by dissociation of one molecule, and has been taken as unity for iodine monochloride.

FIG. 1.

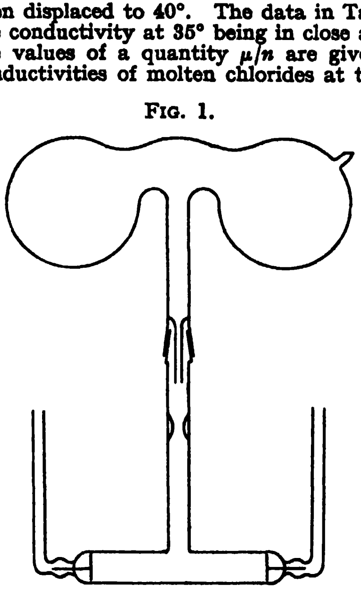
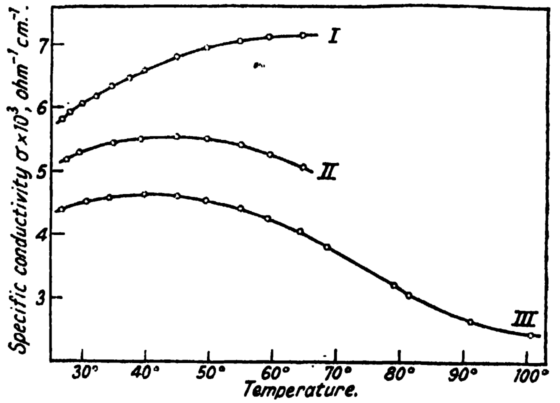


FIG. 2.



Iodine monochloride : I, impure ; II, partly purified ; III, highly purified.

TABLE I.

Conductivity of molten iodine monochloride between 27° and 120°.

Temp.	$\sigma \times 10^3$ (ohm^{-1} cm.$^{-1}$).	Density (d) (g./cm.^{3}).*	$\mu/n = M\sigma/dn$.	Temp.	$\sigma \times 10^3$ (ohm^{-1} cm.$^{-1}$).	Density (d) (g./cm.^{3}).*	$\mu/n = M\sigma/dn$.
26·75°	4·403	3·193	0·2217	64·8°	4·057	3·066	0·2149
30·6	4·519	3·180	0·2309	69·0	3·810	3·052	0·2027
34·45	4·593	3·168	0·2355	79·3	3·271	3·017	0·1760
39·9	4·637	3·149	0·2392	81·8	3·068	3·010	0·1655
45·1	4·610	3·131	0·2392	91·4	2·667	2·977	0·1455
49·7	4·541	3·117	0·2366	101·0	2·471	—	—
55·1	4·415	3·098	0·2314	113·0	2·043	—	—
59·8	4·270	3·082	0·2250	122·0	1·817	—	—

* By interpolation from Hannay's data (*J.*, 1873, 26, 815).

The current–voltage curves obtained in a series of direct-current measurements with iodine monochloride are shown in Fig. 3. Two temperatures were chosen, one above and one below the temperature of maximum conductivity, and in neither case was there any evidence of a decomposition potential. The measurements were extended down to potentials of 1 mv. with the same result. In a parallel experiment, iodine monochloride was electrolysed at 35° in a cell with separate anode and cathode compartments. After a given time the circuit was broken, and the back e.m.f. followed potentiometrically until a steady value had been attained. This having been read, the electrolysis was continued for a further period and the same procedure repeated. Usually, the steady value was attained within 5 minutes of breaking the circuit and was about two thirds of the original value. This back e.m.f. remained constant for one hour. The results are given in Table II. The A.C. resistance of the cell was 24300 ohms, the D.C. voltage 113 v., and the D.C. current 4·65 milliamp. The volume of each electrode compartment was approx. 5 ml. Not only was the back e.m.f. extremely small, but it was also dependent on the amount of electrolysis. An explanation of these effects is presented in the discussion.

TABLE II.

Time of electrolysis (min.)	30	55	178
Faradays passed, $\times 10^4$	0·868	1·59	5·15
Back e.m.f. (mv.)	7	8·5	11

Iodine Trichloride.—Pure iodine trichloride was prepared by adding finely powdered resublimed iodine to an excess of liquid chlorine at −78°. The chlorine had been purified by distillation. The excess of chlorine was allowed to evaporate through a silica drying tower. This material was filled directly into the conductivity cell, which was sealed at atmospheric pressure. The cell was made of Pyrex glass with a 3-mm. wall thickness in order to withstand the high pressure of the molten trichloride at and above its m. p. (101°). This pressure is 16 atm. at 101°. The molten trichloride attacked platinum rapidly but tungsten was not corroded even on prolonged heating. Tungsten rods of 5-mm. diameter were used as electrodes and were ground to 2-mm. diameter where they passed through the glass wall of the cell. The electrical circuit and the thermostatic control were the same as in the experiments on iodine monochloride.

TABLE III.

Conductivity of solid and of liquid iodine trichloride between 70° *and* 150°.

Temp.	70·0°	79·9°	84·8°	89·9°	95·0°	96·2°	97·7°	99·4°	100·1°	102·0°	103·7°	
$\sigma \times 10^3$, ohm^{-1} cm.$^{-1}$	0·0190	0·0597	0·175	0·490	2·64	4·68	6·87	8·25	8·35	8·60	9·13	
Temp.	105·3°	107·0°	109·3°	112·5°	115·0°	122·9°	127·0°	131·0°	135·5°	139·0°	142·7°	146·5°
$\sigma \times 10^3$, ohm^{-1} cm.$^{-1}$	9·31	9·40	9·55	9·53	9·34	8·15	6·73	4·52	2·39	1·29	0·69	0·36

The data in Table III show the results of a typical series of measurements made below and above the m. p. of the trichloride on material previously melted and allowed to solidify. These data show that the conductivity of solid iodine trichloride increases rapidly as the temperature is raised and that there is no pronounced discontinuity at the m. p. Above the m. p. the conductivity rises more slowly, passing through a maximum at 111°. Thereafter the value falls and at 145° is equal to that for the solid 10° below the m. p. The existence of the maximum is conveniently represented by plotting the logarithm of the conductivity against the reciprocal of the absolute temperature, as in Fig. 4. As in the case of iodine monochloride, direct-current measurements gave linear current–voltage plots without any indication of the existence of a decomposition potential.

FIG. 3.

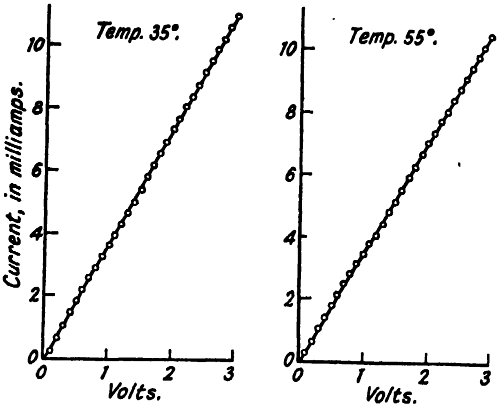
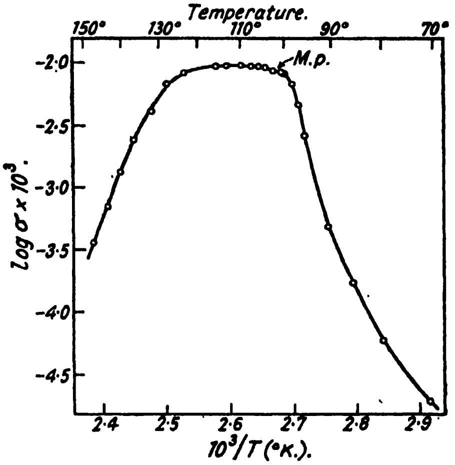


FIG. 4.



DISCUSSION.

The degree of ionisation required to account for the observed conductivity of iodine monochloride may be calculated very approximately, but the necessary data are not available for the trichloride. By extrapolation of Beck's results (*Z. physikal. Chem.*, 1904, **48**, 641) the viscosity (η) of iodine monochloride at 35° is 3·74 centipoises. From the data of Cornog and Karges (*loc. cit.*) the equivalent conductivity at infinite dilution (λ_∞) of potassium chloride in iodine monochloride is 31·7, from which the product $[\eta \,.\, \lambda_\infty]_{\text{KCl in ICl}}$ is 118 The corresponding figure, $[\eta \,.\, \lambda_\infty]_{\text{KCl in H}_2\text{O}}$, for an aqueous solution of potassium chloride, is 136. It would therefore seem that Walden's rule applies approximately, the conductivity of potassium chloride varying inversely as the solvent viscosity. The applicability of Walden's rule may be fortuitous, but experimentally it does hold for the conductivity of potassium chloride in iodine monochloride and in water, and this fact may be used to estimate the ionic mobilities by the following argument.

Fialkov and Kaganskaya (*J. Gen. Chem. Russia*, 1948, **18**, 289) have shown that the ionic species present in a solution of potassium chloride in iodine monochloride are K^+ and $[ICl_2]^-$ and that the transference number of the $[ICl_2]^-$ ion is 0·504, a value which is very close to that for the Cl^- ion in an aqueous solution of potassium chloride. It is therefore possible to estimate the mobility of $[ICl_2]^-$ from the known mobility of Cl^- in aqueous solution ($7{\cdot}9 \times 10^{-4}$ cm./sec. per volt/cm.), as $v_{ICl_2^-} = 7{\cdot}9 \times 10^{-4} \times (\eta_{H_2O}/\eta_{ICl}) \simeq 2 \times 10^{-4}$ cm.^{2}volt^{-1}sec.$^{-1}$. It being assumed to a first approximation that the mobilities of I^+ and ICl_2^- are equal, the average ionic mobility (v) of iodine monochloride may be taken as 2×10^{-4}cm.^{2}volt^{-1}sec.$^{-1}$, a value which is likely to be correct to within a factor of 2. If m is the number of current carriers per c.c. and e is the electronic charge, then as the conductivity at 35° ($\sigma_{35} = mev$) has a value of $4{\cdot}6 \times 10^{-3}$ohm^{-1}cm.$^{-1}$, a value for m of $1{\cdot}4 \times 10^{20}$ carriers/c.c. is obtained. If the value of the density at 35° is taken as $3{\cdot}165$ g.cm.$^{-3}$, 1 c.c. of iodine monochloride contains $1{\cdot}17 \times 10^{22}$ molecules, and the degree of ionisation is therefore $1{\cdot}2 \times 10^{-2}$. Thus, from this approximate calculation, about one in eighty molecules of iodine monochloride is dissociated into ions at 35°, a value which should be correct, at least as far as order of magnitude is concerned.

The specific conductivity data for iodine monochloride show a maximum at 40°. This maximum might arise from opposing density and viscosity effects. The maximum persists, however, when the quantity $\mu/n (= M\sigma/dn)$ is plotted against temperature. This is shown by the data in the last column of Table I. The quantity μ/n has been used by Biltz and Klemm (*loc. cit.*) to compare the conductivity of molten chlorides at their melting points. It effects a correction for the change in the number of conducting species per c.c. arising from the change of density with temperature, and the persistence of the maximum when this correction has been made shows that the maximum is not due to opposing viscosity and density effects. Increase in temperature lowers the viscosity, so that mobilities will tend to increase. This increase can only be counterbalanced by a decrease in ionisation as the temperature is raised.

The appreciable conductivity of iodine trichloride in the solid state is of great interest. The conductivity is of the same order of magnitude as the ionic conductivity of alkali halide crystals near their melting points (Mott and Gurney, " Electronic Processes in Ionic Crystals," p. 36). In these crystals, the conductivity is governed by the number and mobility of the lattice defects. Expressions derived for a conductivity arising from the migration of these defects show a linear dependence of log σ on $1/T$. Such a dependence was not found for iodine trichloride (Fig. 4). It should be emphasised, though, that the method used to measure the conductivity of the solid is not free from criticism. Accurate measurements on the solid would require a more elaborate circuit; the present results are merely presented to show that iodine trichloride in the solid state has a considerable conductivity. At present, the possibility of semiconduction is not definitely ruled out, even though this also would lead to an exponential dependence of the conductivity on $1/T$ in a range where only one conduction process is occurring. Transport experiments on solid iodine trichloride, or thermoelectric measurements, would distinguish between the two possible conduction mechanisms.

An explanation of the extremely small back e.m.f. generated on electrolysing molten iodine monochloride may be based on the hypothesis that the electrode products are already present in the melt, in thermodynamic equilibrium with iodine monochloride. In this case electrolysis would merely alter the concentration of the products at each electrode and a concentration e.m.f. would be set up on electrolysis. The magnitude of this should depend on the amount of electrolysis, and this effect has been observed (Table II).

If one assumes the electrode products are iodine at the cathode, and iodine trichloride at the anode, then, using the published values of free energy for the reactions concerned, it is possible to show that such a hypothesis does, in fact, reproduce the essential features of the back e.m.f. measurements. In addition, the hypothesis would explain why no decomposition potential is observed when D.C. current–voltage measurements are made. As electrolysis merely alters locally the normal equilibrium concentrations of iodine and iodine trichloride in the melt, and since the amount of electrolysis in the current–voltage measurements is considerably less than that used in the back e.m.f. measurements (see Table II), the back potentials developed would be so small as to be undetectable with the precision of measurement used. It is likely that a similar explanation would account for the absence of a decomposition potential in iodine trichloride and bromine trifluoride, though in these cases the nature of the electrode processes is less certain and the requisite thermodynamic data are not available.

The authors are indebted to Professor R. E. Connick for his assistance in the interpretation of the experimental results. One of the authors (N. N. G.) wishes to thank the Commissioners of the Exhibition of 1851 for the award of an Overseas Studentship, during the tenure of which this work was done.

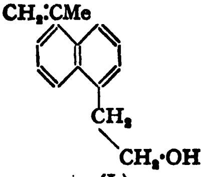
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 14th*, 1949.]

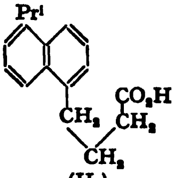
204. *Syntheses in the Phenanthrene Series. Part XI.** 1-*Methyl*-8-iso*propylphenanthrene.*

By W. F. SHORT and H. WANG.

1-Methyl-8-*iso*propylphenanthrene has been synthesised from 1-naphthoic acid viâ 5-bromo-1-naphthoic acid, γ-5-*iso*propyl-1-naphthylbutyric acid, and 1-keto-8-*iso*propyl-1 : 2 : 3 : 4-tetrahydrophenanthrene. It is identical with the hydrocarbon obtained by the dehydrogenation of totarane.

IN attempting the synthesis of 1-*methyl*-8-iso*propylphenanthrene* we first prepared 1-*bromo*-6-iso*propenylnaphthalene* by the action of acetone on 5-bromo-2-naphthylmagnesium bromide (Fieser and Riegel, *J. Amer. Chem. Soc.*, 1937, **59**, 2564) but were unable to obtain an addition product from the unsaturated compound and maleic anhydride. We therefore condensed 1-nitronaphthalene with paraformaldehyde and hydrogen chloride (I.G. Farbenindustrie, B.P. 473,522) and converted the resulting 5-nitro-1-chloromethylnaphthalene into 5-*nitro*-1-*hydroxy*-*thylnaphthalene*, 5-nitro-1-naphthaldehyde (Ruggli and Burckhardt, *Helv. Chim. Acta*, 1940, , 445), 5-nitro-1-naphthoic acid (Ruggli and Burckhardt, *loc. cit.*), and 5-*amino*-1-*naphthoic id.* Satisfactory conditions for the conversion of the amino-acid into 5-bromo-1-naphthoic acid could not be found, and the bromo-compound was therefore prepared by direct bromination of 1-naphthoic acid (Kerkhof, *Rec. Trav. chim.*, 1932, **51**, 747), obtained in 87% yield by the oxidation of 1-naphthyl methyl ketone.


(I.)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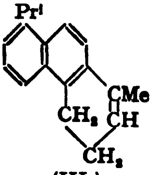
(III.)

1-*Bromo*-5-iso*propenylnaphthalene*, prepared by dehydrating the product of the reaction between *methyl 5-bromo*-1-*naphthoate* and methylmagnesium iodide, could not be reduced to the corresponding *iso*propyl compound owing to preferential removal of the bromine atom. 5-*iso*-Propenyl-1-naphthylmagnesium bromide was therefore brought into reaction with ethylene oxide and the resulting 2-5′-iso*propenyl*-1′-*naphthylethyl alcohol* (I) was reduced to 2-5′-iso*propyl*-1′-*naphthylethyl alcohol*. The corresponding *bromide* and ethyl sodiomalonate afforded *ethyl* 2-5′-iso*propyl*-1′-*naphthylethylmalonate* (59%), which was successively hydrolysed to the acid, m. p. 151—152°, and decarboxylated to γ-5-iso*propyl*-1-*naphthylbutyric acid* (II), m. p. 120—121°. The acid was dehydrated to 1-*keto*-8-iso*propyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*, m. p. 86—87°, by stannic chloride or phosphoric oxide, and the cyclic ketone afforded 1-*methyl*-8-iso*propyl*-3 : 4-*dihydrophenanthrene* (III), m. p. 72—73°, on successive treatment with methylmagnesium iodide and formic acid. The dihydro-compound was smoothly dehydrogenated by chloranil to 1-*methyl*-8-iso*propylphenanthrene*, m. p. 100·5—101°, which is identical with the hydrocarbon obtained by the dehydrogenation of totarane (Short and Stromberg, *J.*, 1937, 519). The consequences of this identity on the structure of totarol are discussed in a forthcoming communication.

EXPERIMENTAL.

1-*Bromo*-6-iso*propenylnaphthalene*.—A mixture of acetone (6 c.c., 1·6 mols.), ether (15 c.c.), and benzene (6 c.c.) was added to a Grignard solution prepared from 1 : 6-dibromonaphthalene (15 g.) (Fieser and Riegel, *loc. cit.*), magnesium (1·5 g.), ether (60 c.c.), and benzene (12 c.c.), and the mixture was boiled for an hour. The unsaturated *bromo*-compound (9·4 g., 73%), b. p. 140—170°/2 mm., was isolated in the usual way and a middle fraction, b. p. 160—165°/3 mm., was analysed (Found : Br, 32·1. $C_{13}H_{11}Br$ requires Br, 32·4%).

5-*Nitro*-1-*chloromethylnaphthalene*.—1-Nitronaphthalene (86·5 g.), paraformaldehyde (37·5 g., 0·55 mol.), anhydrous zinc chloride (37·5 g.), and concentrated hydrochloric acid (15 g.) were stirred at 65—70° for 20 hours, a current of hydrogen chloride being passed into the mixture. The product was poured into water, and the solid was then collected, washed with water to neutrality, pressed to remove oily impurities, and recrystallised twice from carbon tetrachloride, giving 5-nitro-1-chloromethylnaphthalene, m. p. 96—98°, in 57% yield. The preparation was repeated several times, using up to 850 g. of nitronaphthalene per batch, and approx. 1 kg. of the chloromethyl compound was prepared, the average yield being 54%. The I.G. Farbenindustrie (B.P. 473,522) records m. p. 96—97° and states that the yield is 74%.

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* Part X, *J.*, 1939, 787.

5-*Nitro*-1-*hydroxymethylnaphthalene*.—The chloromethyl compound was suspended in approximately 2N-sodium carbonate (1·8 mols.) and, after being boiled under reflux for 48 hours, the mixture was cooled, and the solid was washed with water and crystallised from chloroform giving 5-*nitro*-1-*hydroxymethylnaphthalene*, m. p. 128—129° (Found: C, 65·2; H, 4·35. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4%). The average yield was 65%. 5-Nitro-1-chloromethylnaphthalene (10 g.), anhydrous sodium acetate (5 g., 1·3 mols.), and acetic anhydride (50 c.c., 11·5 mols.) were boiled for 3 hours and worked up. Crystallisation of the solid from ethanol afforded 5-*nitro*-1-*acetoxymethylnaphthalene* (67%), m. p. 90° (Found: C, 63·2; H, 4·7; N, 6·15, 5·9. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

5-*Nitro*-1-*naphthaldehyde and* 5-*Nitro*-1-*naphthoic Acid*.—(*a*) A solution of chromic anhydride (2·5 g.; equiv. to 1·5 atoms of oxygen) in hot acetic acid (75 c.c.) was added during 1½ hour to a stirred solution of the preceding alcohol (5 g.) in acetic acid (50 c.c.), the temperature being kept at 65—70° during the addition and for an hour subsequently. The solution was concentrated to 15 c.c. below 80°, and the residue was washed with dilute hydrochloric acid and water. Extraction with dilute aqueous sodium carbonate removed 5-nitro-1-naphthoic acid (1·1 g., 21%), m. p. 235—237°, and crystallisation of the residue from chloroform then gave 5-nitro-1-naphthaldehyde (1·3 g., 27%), m. p. 134—136°. The *semicarbazone* had m. p. 301—304° (decomp.) (Found: N, 22·4. $C_{12}H_{10}O_3N_4$ requires N, 21·7%). Ruggli and Burckhardt (*loc. cit.*), who nitrated 1-naphthaldehyde, record 136—137° and 236—237° as the m. p. of the nitro-aldehyde and the nitro-acid, respectively, whilst Ekstrand (*J. pr. Chem.*, 1888, **38**, 241) states that the acid has m. p. 239°. When the alcohol (90 g.) was dissolved in acetic acid (900 c.c.) and oxidised at 65—70° with chromic anhydride (75 g.; equiv. to 2·5 atoms of oxygen) in acetic acid (2250 c.c.) no aldehyde was produced and the yield of nitro-acid, m. p. 237—239°, was 51 g. (53%).

(*b*) When a solution of potassium permanganate (4·3 g.; equiv. to 2·05 atoms of oxygen) in water (100 c.c.) was gradually added to a boiling suspension of 5-nitro-1-chloromethylnaphthalene (4·4 g.) in 17% aqueous sodium hydroxide (100 c.c.; 26 mols.) the product consisted of 5-nitro-1-naphthoic acid (0·9 g., 21%) and 5-nitro-1-hydroxymethylnaphthalene (1·8 g. 44%).

5-*Amino*-1-*naphthoic Acid*.—The nitro-acid (7·4 g.) was reduced with a solution of ferrous sulphate heptahydrate (67·5 g., 7·1 mols.) in water (225 c.c.) in the presence of concentrated ammonia (150 c.c.), and the crude amino-acid (5·2 g., 82%) was crystallised from ethanol giving 5-*amino*-1-*naphthoic acid* in orange needles, m. p. 201—202° (Found: N, 7·1. $C_{11}H_9O_2N$ requires N, 7·4%). The *hydrochloride* separated from alcohol in orange needles, m. p. 278—280° (decomp.; rapid heating) (Found: N, 6·2. $C_{11}H_{10}O_2NCl$ requires N, 6·3%).

1-*Naphthyl Methyl Ketone*.—The ketone was prepared by adding a solution of aluminium chloride and acetyl chloride in ethylene chloride to a solution of naphthalene in ethylene chloride at 30—35° and stirring the solution at this temperature for 2—3 hours, according to Baddeley's general directions (*J.*, 1949, S 99). Pure 1-naphthyl methyl ketone has m. p. 10·5° (Lock, *Monatsh.*, 1943, **74**, 77), and no ketone melting below 0° was employed in the preparation of 1-naphthoic acid. A fraction of the ketone, b. p. 132—134°/2 mm., usually melted in the range 2—4°, whereas a higher fraction, b. p. 134—136°/2 mm., melted in the range −5° to 0° and contained some 2-naphthyl methyl ketone. If the higher-boiling fraction was not rejected some sodium 2-naphthoate separated during the preparation of 1-naphthoic acid (below). When naphthalene, aluminium chloride, and acetyl chloride were employed in the molecular ratio 1 : 2 : 2, 2600 g. of naphthalene afforded 2014 g. (58%) of ketone having m. p. >0°, and when the ratio was 1 : 1·1 : 1·3, 676 g. of naphthalene gave 574 g. (64%) of ketone of this quality. The yield of ketone, b. p. 134—136°/2 mm. was *ca.* 10%.

1-*Naphthoic Acid*.—1-Naphthyl methyl ketone was oxidised with alkaline sodium hypochlorite essentially according to the method of Fieser, Newman, and Holmes (*J. Amer. Chem. Soc.*, 1936, **58**, 1055. Compare Newman and Holmes, *Org. Synth.*, 1937, **17**, 65; Coll. Vol. II, 1943, 428). A solution 1·6M. with respect to sodium hypochlorite and 0·54N. with respect to sodium hydroxide was prepared from technical sodium hypochlorite solution (2·6—2·8M.), sodium hydroxide and water, and 3125 c.c. of this solution (containing 5 mols. of sodium hypochlorite and 1·7 mols. of sodium hydroxide) were used for the oxidation of 170 g. of the ketone. A large flask is necessary since there is considerable frothing during the liberation of chloroform, and efficient stirring is essential. Metal stirrers should not be used since they cause decomposition of the hypochlorite and promote the formation of chloronaphthoic acid. An exothermic reaction occurred when the mixture was stirred vigorously at 55° and the temperature was maintained at 60—65° by occasionally cooling in ice-water during this phase (40 minutes). The mixture was stirred at 60—65° for another 30 minutes and excess of hypochlorite was then destroyed by adding aqueous sodium hydrogen sulphite. (If the ketone was contaminated with the 2-isomer a little sodium 2-naphthoate separated on cooling the solution.) The solution was acidified with concentrated hydrochloric acid, and the solid was collected, washed with water, and crystallised once from aqueous ethanol. The 1-naphthoic acid had m. p. 149—152° and was sufficiently pure for use in subsequent operations; the pure acid has m. p. 160°. 1500 G. of 1-naphthoic acid were prepared in this way and the average yield was 87%.

5-*Bromo*-1-*naphthoic Acid*.—An improved yield of this acid was obtained by modifying Kerkhof's method (*loc. cit.*). A solution of 1-naphthoic acid (200 g.) in glacial acetic acid (500 c.c.) was heated on the steam-bath and stirred during the addition of bromine (60 c.c., 1·01 mols.). A yellow solid separated during the addition (1 hour), and, after being heated and stirred for another 1½ hours and kept overnight at room temperature, the solid was crystallised from acetic acid (2000 c.c.). The average yield in the preparation of 920 g. of bromo-acid was 56% and this product, which melted within the range 252—255°, was used in subsequent experiments. Recrystallisation from acetic acid and methanol raised the m. p. to 256—256·5°; Kerkhof (*loc. cit.*) records m. p. 261°, and Ruggli and Preuss (*Helv. Chim. Acta*, 1941, **24**, 1359), m. p. 245—247°. A complex mixture of bromo-acids was precipitated when the filtrates were diluted with water.

Methyl 5-*Bromo*-1-*naphthoate*.—(*a*) Methyl sulphate (240 c.c., 4·2 mols.) was slowly added to a stirred solution of the bromo-acid (150 g.) and sodium hydroxide (30 g., 1·25 mols.) in water (600 c.c.) and methanol (600 c.c.). The mixture was stirred at room temperature for 3 hours, heated to the b. p. on the steam-bath, cooled, and made alkaline with aqueous sodium carbonate. The solid was collected, and unchanged acid (43%), m. p. 251—254°, was recovered from the alkaline solution. After being washed with water and dried, the crude ester (49%) had m. p. 64—65°, and crystallisation from methanol afforded *methyl 5-bromo-1-naphthoate* in needles, m. p. 66—67° (Found: Br, 30·0. $C_{12}H_9O_2Br$ requires Br, 30·2%). The ester sublimes readily but can be distilled; b. p. 268—274°/215 mm., 170—175°/3·5 mm. (*b*) When dry powdered potassium 5-bromo-1-naphthoate (5·8 g.) and methyl sulphate (3 c.c., 1·6 mols.) were heated at 200—210° for 1 hour the yield of ester was 3·3 g. (62·5%), but no acid was recovered.

1-*Bromo*-5-iso*propenylnaphthalene*.—A solution of methyl 5-bromo-1-naphthoate (265 g.) in ether (1200 c.c.) was added during 1½ hours to an ice-cold solution of methylmagnesium iodide (2·4 mols.), prepared from magnesium (57·5 g.), methyl iodide (148 c.c.), and ether (400 c.c.). After being stirred overnight at room temperature and boiled for 1 hour, the complex was decomposed and the crude product was distilled with powdered potassium hydrogen sulphate (50 g.) giving the crude bromonaphthalene, b. p. 140—150°/3—4 mm. The average yield was 54% and there was occasionally a fraction of higher b. p. which solidified on cooling and consisted of unchanged methyl 5-bromo-1-naphthoate (5—10%). A middle fraction, b. p. 138—140°/2 mm., of the 1-*bromo*-5-iso*propenylnaphthalene* was analysed (Found: C, 62·7; H, 4·5. $C_{13}H_{11}Br$ requires C, 63·1; H, 4·5%). The *picrate* separated from alcohol in yellow needles, m. p. 94—95° (Found: N, 9·0. $C_{13}H_{11}Br,C_6H_3O_7N_3$ requires N, 8·8%).

2-5′-iso*Propenyl*-1′-*naphthylethyl Alcohol*.—1-Bromo-5-*iso*propenylnaphthalene is reluctant to react with magnesium, and when methyl iodide or ethyl bromide was used as entrainer, subsequent reaction with ethylene oxide afforded very low yields of the desired alcohol, and hydrocarbons were produced in considerable quantity, analyses suggesting that bromine had been partly replaced by methyl and ethyl, respectively. When Gilman and Kirby's iodine-activated magnesium (*Rec. Trav. chim.*, 1935, **54**, 577) was used, a 43% yield of the alcohol was obtained but it was not possible to use a small amount of this activated magnesium to promote reaction of the halide with ordinary magnesium. Much better results were obtained by using preformed ethylmagnesium bromide as catalyst, the reaction being carried out in an atmosphere of dry nitrogen.

A solution of 1-bromo-5-*iso*propenylnaphthalene (175 g.) in dry ether (700 c.c.) was added during 4 hours to an ice-cold, stirred suspension of magnesium in ethereal ethylmagnesium bromide prepared from magnesium (36 g., 2·1 atoms), ethyl bromide (52·5 c.c., 1 mol.), and ether (440 c.c.). After the mixture had been stirred overnight and boiled under reflux for 1 hour, it was cooled to 0°, and a 25% (w/v) solution of ethylene oxide in dry benzene (520 c.c.; 4·2 mols.) was introduced during 3 hours. The mixture was then boiled under reflux for an hour, the ether was removed by distillation, and the residue, still containing most of the benzene, was cooled and decomposed with ice-cold dilute hydrochloric acid. The alcohol was purified by distillation, the fraction, b. p. 152—158°/1 mm., being collected (average yield, 74%). 2-5′-iso*Propenyl*-1′-*naphthylethyl alcohol* was a colourless, viscous liquid; a fraction, b. p. 153—154°/1 mm., was analysed (Found: C, 83·4, 83·6; H, 7·3, 7·4. $C_{15}H_{16}O$ requires C, 84·9; H, 7·55%). 2-5′-iso*Propenyl*-1′-*naphthylethyl* p-*diphenylylcarbamate* crystallised from benzene–light petroleum in colourless needles, m. p. 147—148° (Found: C, 82·3; H, 6·2; N, 3·5. $C_{28}H_{25}O_2N$ requires C, 82·5; H, 6·15; N, 3·4%). Some of the earlier preparations of the alcohol afforded a small fraction, b. p. 165—220°/2 mm., which solidified and afforded crystals, m. p. 183—184°, after crystallisation from alcohol, probably of 5 : 5′-*di*iso*propenyl*-1 : 1′-*dinaphthyl* (Found: C, 92·7; H, 6·5. $C_{26}H_{24}$ requires C, 92·9; H, 7·0%).

2-5′-iso*Propyl*-1′-*naphthylethyl Alcohol*.—The unsaturated alcohol (75 g.) was readily reduced when dissolved in methanol (750 c.c.) and shaken with palladium–strontium carbonate (30 g.; 1·2% Pd) in hydrogen at room temperature and atmospheric pressure. Absorption of hydrogen was complete in 5 hours and the average yield of alcohol, m. p. 60—62°, b. p. 158—164°/1·5 mm., was 74%. 2-5′-iso*Propyl*-1′-*naphthylethyl alcohol* separated from light petroleum (b. p. 40—60°) in cubes, m. p. 63—64° (Found: C, 83·7; H, 8·1. $C_{15}H_{18}O$ requires C, 84·1; H, 8·4%). 2-5′-iso*Propyl*-1′-*naphthylethyl* p-*diphenylylcarbamate* had m. p. 161° (Found: C, 81·6; 81·8; H, 6·5, 6·55; N, 3·7. $C_{28}H_{27}O_2N$ requires C, 82·1; H, 6·6; N, 3·4%), and 2-5′-iso*propyl*-1′-*naphthylethyl acetate* had b. p. 164—166°/1 mm., m. p. 33—34° (Found: C, 79·4; H, 7·9. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%).

2-5′-iso*Propyl*-1′-*naphthylethyl Bromide*.—Phosphorus tribromide (2·2 c.c., 0·5 mol.) was added to a solution of the alcohol (10 g.) in carbon tetrachloride (10 c.c.) at 50°, and, after being kept at 50—60° for ½ hour, the solution was poured into ice-water. The *bromide* had b. p. 131—135°/0·2 mm., and separated from light petroleum (b. p. 40—60°) in plates, m. p. 41—42° (Found: C, 65·9, 65·75; H, 6·3, 6·0; Br 29·0. $C_{15}H_{17}Br$ requires C, 65·0; H, 6·1; Br, 28·9%). The average yield was 50·5%.

2-5′-iso*Propyl*-1′-*naphthylethylmalonic Acid*.—A solution of ethyl malonate (81 g., 2 mols.) in dry xylene (130 c.c.) was added to a sodium methoxide solution prepared from sodium (7 g., 1·2 atoms) and methanol (100 c.c.), and most of the solvents was removed by distillation under reduced pressure below 80°. A solution of the preceding bromide (70 g.) in xylene (115 c.c.) was then added slowly with stirring, and the temperature was slowly raised to 140—150° (oil-bath). After 16 hours at this temperature the products were isolated; 45% of the ethyl malonate was recovered and the average yield of the substituted malonic ester, b. p. 190—195°/0·5 mm., was 59%. A solution of the malonic ester (10 g.) in methanol (10 c.c.) was added to a solution of potassium hydroxide (8·15 g., 4·4 mols.) in water (10 c.c.), and, when the vigorous reaction had subsided, water (40 c.c.) was added, and the hydrolysis was completed by heating the solution on the steam-bath for 3 hours. The crude malonic acid, m. p. 149—151° (decomp.), was isolated, the average yield being 86%. Recrystallisation of this from acetic acid or benzene afforded 2-5′-iso*propyl*-1′-*naphthylethylmalonic acid* in white plates, m. p. 151—152° (decomp.) (Found: C, 72·3; H, 6·7. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

γ-5-iso*Propyl*-1-*naphthylbutyric Acid*.—This acid was obtained in 91% yield when the malonic acid was heated at 155—165° for 2 hours and the residue was crystallised from light petroleum (b. p. 60—80°). The pure *acid* crystallised from light petroleum in plates or needles, m. p. 120—121° (Found: C, 78·7, 79·0; H, 7·8, 7·8%; *M*, by titration, 256, 255. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%; *M*, 256).

1-*Keto*-8-iso*propyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*.—(*a*) The butyric acid (10 g.), phosphoric oxide (50 g., 9 mols.), and benzene (150 c.c.) were heated under reflux for 3 hours, and the product was worked up as described in previous parts of the series. The neutral fraction, b. p. 165—172°/0·3 mm., solidified on cooling giving the crude ketone, m. p. 81—84° (36%), crystallisation of which from light petroleum afforded 1-*keto*-8-iso*propyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene* in colourless needles, m. p. 86—87° (Found : C, 85·3; H, 7·6. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%). The *semicarbazone* crystallised from alcohol in colourless prisms, m. p. 246—247° (decomp.) (Found : N, 14·2. $C_{18}H_{21}ON_3$ requires N, 14·2%). The crude ketone isolated from the mother liquors afforded the same semicarbazone, showing that no isomeric ketone is produced in the ring closure. Only a trace of unchanged acid was recovered. (*b*) A mixture of the butyric acid (3 g.) and stannic chloride (3·9 c.c., 2·8 mols.) was heated at 105—110° for 1½ hours with frequent shaking, cooled, and decomposed with ice-cold dilute hydrochloric acid. After removal of unchanged acid, m. p. 117—119° (15%), the ketone (60%) solidified without distillation and was obtained pure, m. p. and mixed m. p. 86—87°, after one crystallisation from light petroleum.

1-*Methyl*-8-iso*propyl*-3 : 4-*dihydrophenanthrene*.—A solution of the cyclic ketone (5 g.) in ether (70 c.c.) was added at room temperature to a solution of methylmagnesium iodide (3 mols.), prepared from magnesium (1·5 g.), methyl iodide (4·3 c.c.), and ether (50 c.c.), and, after being boiled under reflux for 3 hours, the product was isolated. The dehydration of the crude carbinol was completed by boiling it for ½ hour with 100% formic acid (10 c.c.) and the crude hydrocarbon, b. p. 165—170°/1 mm., was purified by crystallisation from methanol, giving white plates of 1-*methyl*-8-iso*propyl*-3 : 4-*dihydrophenanthrene* (3·3 g.; 67%), m. p. 72—73° (Found : C, 91·5; H, 8·7. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%).

1-*Methyl*-8-iso*propylphenanthrene*.—A solution of the dihydrophenanthrene (1·5 g.) and chloranil (1·57 g., 1 mol.) in sulphur-free xylene (7 c.c.) was boiled under reflux until no colour reaction for chloranil was obtained (20 hours). The solution was cooled to 0° and filtered from tetrachloroquinol, and the filtrate was diluted with ether, washed with 5% aqueous potassium hydroxide, dried ($MgSO_4$), and evaporated. The residue was crystallised several times from methanol (charcoal) giving 1-*methyl*-8-iso*propylphenanthrene* (0·4 g.) in white plates, m. p. 100·5—101° (Found : C, 92·0; H, 7·8. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%). The material recovered from the mother liquors was distilled from sodium under reduced pressure, and the fraction, b. p. 180—185°/2 mm., which solidified on cooling, was crystallised from ethanol giving 0·51 g. of hydrocarbon, m. p. 99—100° (total yield, 61%). The *picrate* crystallised from alcohol in orange-yellow needles, m. p. 142—142·5° (Found: C, 62·9; H, 4·4; N, 9·25. $C_{18}H_{18},C_6H_3O_7N_3$ requires C, 62·3; H, 4·5; N, 9·1%), and the *styphnate* in yellow needles, m. p. 152·5—153° (Found : C, 61·2, 61·1; H, 4·5, 4·4; N, 9·0. $C_{18}H_{18},C_6H_3O_8N_3$ requires C, 60·2; H, 4·4; N, 8·8%). Oxidation of the hydrocarbon (0·2 g.) in acetic acid (3 c.c.) with chromic anhydride (0·26 g. in 0·5 c.c. of water and 1·5 c.c. of acetic acid), the mixture being heated finally on the steam-bath for 10 minutes, afforded 1-*methyl*-8-iso*propylphenanthra*-9 : 10-*quinone* which separated from acetic acid in orange rods, m. p. 163·5—164° (Found : C, 81·4; H, 6·1. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). A specimen of the quinone was converted into 1′-*methyl*-4″-iso*propyl*-1 : 2 : 3 : 4-*dibenzphenazine*, which crystallised from ethanol–chloroform in pale yellow rods, m. p. 153·5—154° (Found : N, 8·05. $C_{24}H_{20}N_2$ requires N, 8·3%).

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RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.
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205. *Hydrogen Chloride–Aluminium Chloride as an Agent of Isomerisation.*

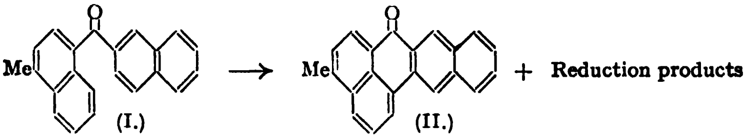
By G. BADDELEY.

Hydrogen chloride catalyses the Scholl reaction and the intramolecular migration of alkyl groups in phenol homologues, aromatic ketones, and aromatic hydroxy-ketones, in the presence of aluminium chloride. These reactions do not occur, or occur at greatly reduced rates, when a stream of dry oxygen or nitrogen is passed through the reaction mixtures. The significance of these results is discussed.

MANY reactions effected by aluminium chloride and other Friedel–Crafts reagents do not occur in the absence of hydrogen chloride or traces of water—for instance, the polymerisation of olefins in the presence of aluminium chloride (Thomas and Carmody, *J. Amer. Chem. Soc.*, 1933, **55**, 3854; Ipatieff and Grosse, *ibid.*, 1936, **58**, 915; Waterman and Leendertse, *J. Inst. Petr. Tech.*, 1938, **24**, 16). Polymerisation of *iso*butene by boron fluoride requires the presence of moisture or, in general, a substance YH capable of forming a strong acid BF_3,YH (A. G. Evans and Polanyi, *J.*, 1947, 252). Other Friedel–Crafts catalysts are subject to the same limitation (Plesch, Polanyi, and Skinner, *J.*, 1947, 257). Reactions of olefins with *iso*paraffins and aromatic hydrocarbons (Ipatieff and Grosse, *J. Amer. Chem. Soc.*, 1935, **57**, 1616; *J. Org. Chem.*, 1937, **1**, 559), isomerisation of paraffins and *cyclo*paraffins (Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold, 1941; Leighton and Heldman, *J. Amer. Chem. Soc.*, 1943, **65**, 2276; Heldman, *ibid.*, 1944, **66**, 1786), and decomposition of paraffins into higher- and lower-boiling hydrocarbons (Ipatieff and Grosse, *Ind. Eng. Chem.*, 1934, **26**, 461) are other reactions effected by aluminium chloride in the presence of hydrogen chloride.

Reversible intramolecular migration of methyl groups in phenol homologues (*J.*, 1943, 527), and irreversible intramolecular migration of methyl and ethyl groups in aromatic ketones (*J.*, 1944, 232) and in aromatic hydroxy-ketones (*J.*, 1943, 273), were caused by aluminium chloride in the presence of hydrogen chloride normally generated when the reactants were brought together in such a manner as to provide homogeneous reaction mixtures. To show whether hydrogen chloride promotes these reactions it is necessary to displace it from the reaction mixtures and to observe whether the rates of isomerisation are adversely affected.

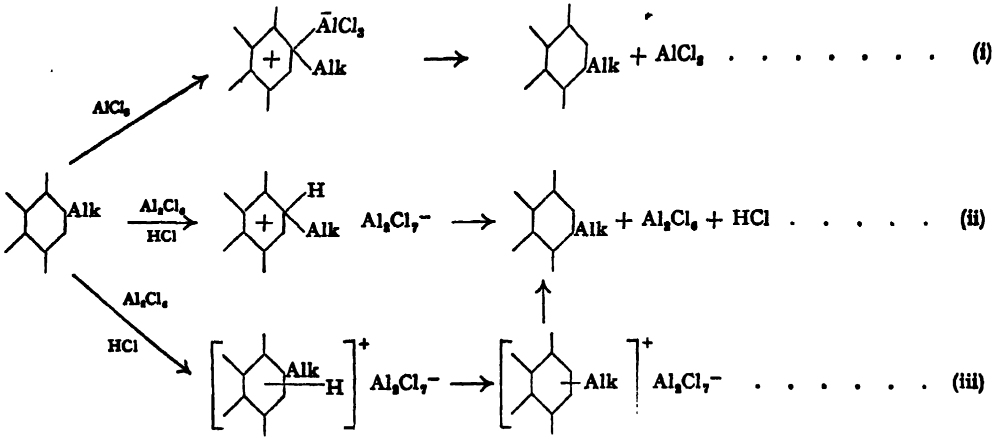
4-Methyl-1 : 2′-dinaphthyl ketone (I), in solution in chlorobenzene, is readily converted (70% yield) at room temperature into 4-methyl-9′ : 10′-benz*meso*benzanthrone (II) by the



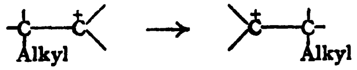
addition of more than a molecular proportion of aluminium chloride (cf. Buckley, *J.*, 1945, 561, 564). This can be considered as a disproportionation; when dry oxygen was passed through the reaction mixture in an attempt to improve the yield of (II), hydrogen chloride was swept from the mixture, and reaction did not occur; a stream of dry nitrogen had the same effect and in each case the reaction commenced when hydrogen chloride was introduced. The more conventional Scholl reaction, in which, for example, 1-benzoylnaphthalene is converted in 70% yield into benzanthrone by fusion with more than two molecular proportions of aluminium chloride at *ca.* 125°, also requires the presence of hydrogen chloride and did not occur when dry oxygen or nitrogen was passed through the molten mixture; addition of sodium chloride and consequent formation of $NaAlCl_4$ did not promote the reaction. These observations, a full account of which will be submitted in a later paper, indicated not only that the presence of hydrogen chloride is essential for the occurrence of the Scholl reaction, but also that a stream of dry nitrogen or oxygen can effectively remove hydrogen chloride from liquid mixtures containing aluminium chloride.

An expeditious and decisive method was now available for demonstrating whether the presence of hydrogen chloride is also necessary in the intramolecular migration of alkyl groups in the benzene derivatives indicated above. As a result of the earlier work on the kinetics of these reactions, homogeneous reaction mixtures of low viscosity were obtained at temperatures well below those required for isomerisation; almost all the hydrogen chloride was swept out with dry nitrogen, and the reaction mixtures were then kept at temperatures adequate for isomerisation. For example, after hydrogen chloride had been removed from a mixture of *p*-cresol and aluminium chloride at 85°, isomerisation did not occur at 135°. Under comparable conditions, but in the presence of hydrogen chloride, the 2 : 3 equilibrium mixture of *p*- and *m*-cresol was obtained. The isomerisation of acetophenone homologues is accompanied by some decomposition and consequent evolution of hydrogen chloride: a stream of dry nitrogen markedly increased the rate of decomposition of 2 : 4-dimethylacetophenone, and hydrogen chloride could not be rigorously excluded at 135°, the temperature of isomerisation. The continuous removal of hydrogen chloride had, however, an adverse effect on the rate of isomerisation. Aromatic *o*-hydroxy-ketones are more resistant to decomposition and 6-hydroxy-2 : 4-dimethylpropiophenone, which can be quantitatively converted into 6-hydroxy-3 : 4-dimethylpropiophenone, did not isomerise after hydrogen chloride had been removed. As all these isomerisations require the presence of hydrogen chloride, it is necessary to state that the reaction mixtures employed in the earlier kinetic studies were in an atmosphere of hydrogen chloride at atmospheric pressure.

So far it has not been possible to demonstrate that hydrogen halide promotes the isomerisation of *p*-xylene in the presence of aluminium halide, as aluminium halide does not combine with the hydrocarbon in the absence of a third component such as hydrogen halide. Norris *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 1163, 2131; 1940, **62**, 1298, 1428) have prepared ternary complexes by passing hydrogen halide into a mixture of aromatic hydrocarbon and aluminium halide and, although they appear to have converted these into binary complexes by elimination of hydrogen halide under reduced pressures, Mr. Voss has found in this laboratory that a stream of dry nitrogen does not wholly remove the hydrogen bromide from its ternary complexes with aluminium bromide and *m*- or *p*-xylene. Aluminium and hydrogen halides do not interact and their combined action on aromatic hydrocarbons, which at low temperatures exhibit weak basic properties towards hydrogen chloride (Brown and Brady, *ibid.*, 1949, **71**, 3573), can be represented by: $ArH + HX + Al_2X_6 \longrightarrow ArH_2^+ + Al_2X_7^-$. This is in accord with the hydrogen exchange observed when deuterium chloride is passed into a mixture of benzene and aluminium chloride (Kenner, Polanyi, and Szego, *Nature*, 1935, **135**, 267), and when applied to the migration of alkyl groups in benzene derivatives leads to mechanism (ii) or (iii) instead of (i) which was previously proposed.


$\bar{A}lCl_3$
Alk
AlCl_3
Alk
+ AlCl_3 . . . . (i)
Alk
Al_2Cl_6
HCl
H
Alk
Al_2Cl_7^-
Alk
+ Al_2Cl_6 + HCl . . . . . (ii)
Al_2Cl_6
HCl
Alk
H
Al_2Cl_7^-
Alk
Al_2Cl_7^- . . . . (iii)

As previously emphasised (Baddeley, *loc. cit.*), the essential feature of all these isomerisations is the formation of a carbonium ion, followed by a rearrangement of the Wagner and Meerwein type:



and subsequently the isomerisation of paraffins and *cyclo*paraffins has been shown to involve intramolecular rearrangement of carbonium ions. Traces of alkyl or *cyclo*alkyl halide in the presence of aluminium halide or of olefin in the presence of both aluminium and hydrogen halides (Pines *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 153; 1948, **70**, 1742) or of sulphuric acid (Burwell and Gordon, *ibid.*, 1948, **70**, 3128) provide carbonium ions (R^+) which initiate chain reactions resulting in isomerisation:

$$\begin{aligned} R^+ + AlkH &\longrightarrow RH + Alk^+ \\ Alk^+ &\rightleftharpoons Alk_1^+ \\ Alk_1^+ + AlkH &\rightleftharpoons Alk_1H + Alk^+ \end{aligned}$$

This mechanism is in accord with the rapid conversion of *tert.*-butyl bromide and *iso*pentane into *iso*butane and *tert.*-amyl bromide in the presence of aluminium bromide (Bartlett, Condon, and Schneider, *ibid.*, 1944, **66**, 1531), and with the observation (Ipatieff, *ibid.*, 1949, **71**, 749) that benzene, by combining with alkyl cations, inhibits the isomerisation of methyl*cyclo*pentane by the combined action of *sec.*-butyl bromide and aluminium bromide. Aluminium and hydrogen bromides do not combine in *n*-butane or *n*-hexane (Fontana and Herold, *ibid.*, 1948, **70**, 2281) and it is not surprising therefore that hydrogen halide does not promote the interconversion of *cyclo*hexane and methyl*cyclo*pentane in the presence of aluminium halide (Stevenson and Beeck, *ibid.*, 1948, **70**, 2890).

EXPERIMENTAL.

A mixture of *p*-cresol (64 g.) and freshly sublimed aluminium chloride (180 g.) was kept at 120—125° (oil-bath) for 15 minutes and subsequently at 90° for 30 minutes. The clear pale brown liquid was decanted from undissolved chloride into two vessels which were placed in a thermostat at 90°. One was fitted with a drying ($CaCl_2$) tube and the other (*A*) with a sintered-glass gas distributor through which dry (P_2O_5) nitrogen at the temperature of the thermostat was passed at a rate of 30 c.c. per minute. The escaping gases were passed through a large plug of glass wool to remove aluminium chloride, a drying ($CaCl_2$) tube, and a bubbler containing water. After several hours, the gases escaping in the following hour neutralised 1·0 c.c. of N/10-sodium hydroxide. The reaction mixtures were then kept at 135° for 9 hours. The amount of hydrogen chloride in the escaping gases remained small. The mixtures were decomposed with ice and dilute hydrochloric acid, and the cresol isolated. That obtained from the mixture (*A*) was nearly pure *p*-cresol (m. p. 31°; mixed m. p. 33°); the other did not solidify at 0° and contained *m*- (60%) and *p*-cresol (40%) (bromate analysis, *loc. cit.*).

A mixture of 2 : 4-dimethylacetophenone (50 g.) and aluminium chloride (100 g.) was heated at 100° for 15 minutes and the homogeneous solution decanted into two vessels. Subsequent procedure was as above. At 135° the mixture (*B*), from which considerable quantities of hydrogen chloride were continuously removed by nitrogen, became much darker than the other. The latter, on decomposition with ice and dilute hydrochloric acid, provided 3 : 4-dimethylacetophenone (semicarbazone, m. p. and mixed m. p. 235°) which contained very little initial ketone (separated by the greater solubility of its semicarbazone in ethanol). The product from (*B*) contained a considerable amount of tar, and the steam-volatile material was a mixture of approximately equal amounts of 2 : 4- and 3 : 4-dimethylacetophenone.

The procedure with 6-hydroxy-2 : 4-dimethylpropiophenone was similar. The reaction mixture was obtained from *m*-5-xylenyl propionate (55 g.), aluminium chloride (126 g.), and sodium chloride (12 g.). Samples which were removed after 5 hours at 85° gave pure 6-hydroxy-2 : 4-dimethylpropiophenone. The nitrogen emitted in an hour now contained an amount of hydrogen chloride which neutralised 0·5 c.c. of N/10-sodium hydroxide, which was increased to 15 c.c. when the temperature was raised to 140°, the reaction mixture becoming much darker than when hydrogen chloride was not removed. These mixtures provided 6-hydroxy-2 : 4- (m. p. and mixed m. p. 75°) and 6-hydroxy-3 : 4-dimethylpropiophenone (m. p. and mixed m. p. 60°) respectively. The former was separated from tar by distillation with steam.

The author is indebted to Professor J. Kenner, F.R.S., for many helpful discussions.

The College of Technology, Manchester, 1. [*Received, January 5th*, 1950.]

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206. *Aromatic Sulphonation. Part I. The Ionisation Constants of* p-*Nitrotoluene, Nitrobenzene, and* p-*Chloronitrobenzene, and the Acidity Function of Oleum.*

By J. C. D. Brand.

The ionisation constants (pK_a) of *p*-nitrotoluene (−10·28), nitrobenzene (−11·26), and *p*-chloronitrobenzene (−11·49) have been determined spectrometrically, and the acidity-function scale of sulphuric acid has been extended into oleum containing up to 14% of sulphur trioxide.

Aromatic mononitro-compounds are weak, although not unobservably weak, bases and their ionisation can be measured in a strongly acidic medium. This basic property was first noticed by Hantzsch (*Z. physikal. Chem.*, 1908, **65**, 41) who found that *p*-nitrotoluene lowered the freezing point of sulphuric acid more than did a non-electrolyte and concluded that the *p*-nitrotoluene was partly converted into an oxonium salt. Cherbuliez (*Helv. Chim. Acta*, 1923, **6**, 281) and Masson (*J.*, 1931, 3200) showed independently that the conductivity of anhydrous sulphuric acid was enhanced by dissolved nitrobenzene and successfully prepared a crystalline addition product, regarded as the hydrogen sulphate, $[C_6H_5{\cdot}NO_2H]^+SO_4H^-$. The ionisation of nitrobenzene in sulphuric acid was confirmed cryoscopically by Treffers and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 1708), and Gordy and Stanford (*J. Chem. Physics*, 1940, **8**, 170) estimated the order of magnitude of the ionisation constant from a comparison of the frequency of the O–D stretching vibration of methyl deuteroalcohol in benzene and nitrobenzene solution.

In the present series of measurements, the degree of ionisation of *p*-nitrotoluene, nitrobenzene, and *p*-chloronitrobenzene was determined spectrometrically in media of successively increasing sulphuric acid concentration. If the ion and free base are assumed to absorb independently, the extinction coefficient (ε) of a solution containing both forms is $\varepsilon = \varepsilon_{BH^+}[BH^+] + \varepsilon_B[B]$, where ε_{BH^+} and ε_B, $[BH^+]$ and $[B]$, are respectively the extinction coefficients (at a particular wave-length) and the relative concentrations of the ion and free base. Because $[BH^+] + [B] = 1$ this equation can be written as $[B]/[BH^+] = (\varepsilon_{BH^+} - \varepsilon)/(\varepsilon - \varepsilon_B)$, which enables the indicator-ionisation ratio to be evaluated directly from the absorption measurements. The ionisation ratio is related to the ionisation constant of the base and the acidity function of the medium by the equation (Hammett, *Chem. Reviews*, 1935, **16**, 67):

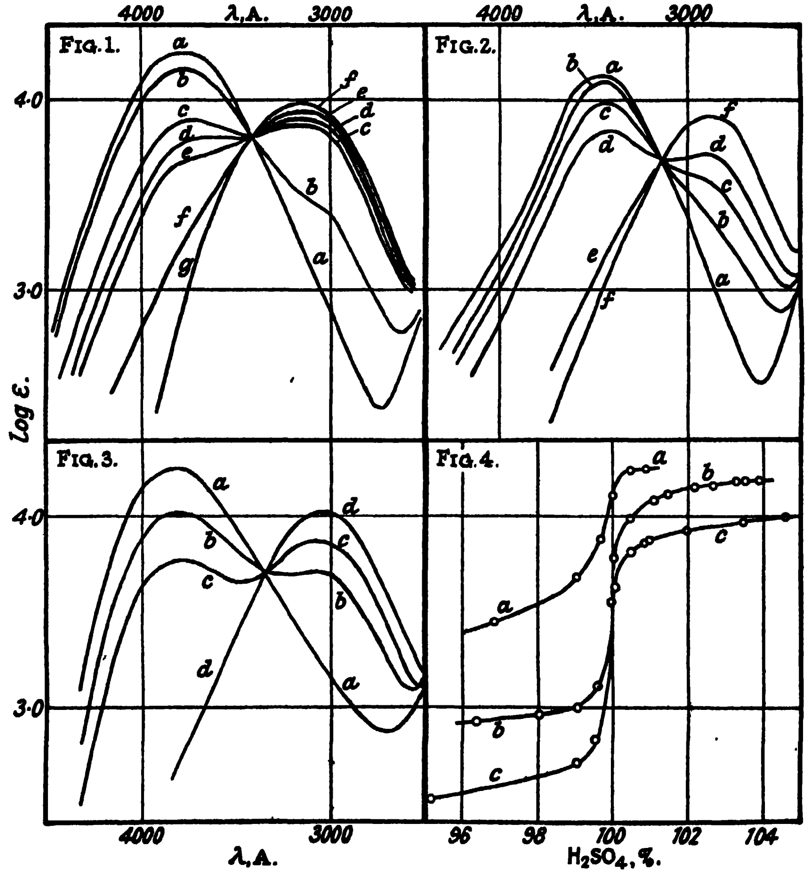
$$H_0 = pK_a + \log [B]/[BH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where K_a is the acidic ionisation constant of the ion BH^+ and H_0 is the acidity function of the medium with respect to an uncharged base. The acidity function of sulphuric acid up to 100% has been determined (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827), and by combining these results with a cryoscopic measurement of the degree of ionisation Hammett (*J. Chem. Physics*, 1940, **8**, 644) found pK_a −11 for nitrobenzene. An improved determination by the same method (Gillespie and Millen, *Quart. Reviews*, 1948, 292) * gave pK_a −11·0. The measurements now reported yield the following values for pK_a:

p-Nitrotoluene	−10·28	*p*-Chloronitrobenzene	−11·49
Nitrobenzene	−11·26		

Although the ionisation constants are in the expected order, the large effect of the *p*-methyl compared with that of the *p*-chloro-substituent is unusual. The result suggests that the transfer

Absorption spectra of p-*nitrotoluene, nitrobenzene and* p-*chloronitrobenzene in sulphuric acid.*



p-*Nitrotoluene.* *Nitrobenzene.*

p-*Chloronitrobenzene.* *Variation of ε with acid composition, λ = 3650 A.*

FIG. 1.

	Acid, %.
a	(*calc.*).
b	100·00
c	99·70
d	99·36
e	99·08
f	96·86
g	85·5

FIG. 2.

	Acid, %.
a	103·2
b	100·8
c	100·24
d	100·02
e	99·0
f	95·2

FIG. 3.

	Acid, %.
a	103·54
b	100·46
c	100·06
d	99·05

FIG. 4.

a	p-*Nitrotoluene*
b	p-*Chloronitrobenzene*
c	*Nitrobenzene*

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* The authors appear to use the original acidity-function scale, which is 0·29 unit higher (less negative) than the scale adopted in this paper (Hammett and Paul, *loc. cit.*).

TABLE I.

Evaluation of ionisation constants and acidity function (*temp.* 21° ± 3°).

Medium.		Extinction coefficient, ε.	$-\frac{1}{\varepsilon}\frac{d\varepsilon}{dt}$ % per min.	log [B]/[BH⁺].	Acidity function,* H_0.	Ionisation constant, pK_a.
% H_2SO_4.	% SO_3.					
A. *Nitrobenzene*, ε_{ion} = 9000, ε_{base} = 300 *at* λ 3650 A.						
84·6	—	203	—	—	—	—
87·6	—	231	—	—	—	—
90·76	—	254	—	—	—	—
95·10	—	329	—	2·5	−8·8	−11·3
99·02	—	507	—	1·61	−9·61	−11·22
99·07	—	511	—	1·61	−9·64	−11·25
99·10	—	505	—	1·62	−9·65	−11·27
99·50	—	686	—	1·34	−9·91	−11·25
99·51	—	686	—	1·34	−9·92	−11·26
99·53	—	693	—	1·33	−9·93	−11·26
99·55	—	664	—	1·36	−9·94	−11·30
						−11·26 ± 0·02
100·05	—	4,320	—	0·08	−11·18	—
100·06	—	4,080	—	0·10	−11·16	—
100·08	—	4,230	—	0·08	−11·18	—
100·09	—	4,350	—	0·06	−11·20	—
100·46	2·04	6,530	0·01	−0·40	−11·66	—
100·51	2·26	6,580	0·02	−0·41	−11·67	—
100·87	3·86	7,250	0·03	−0·60	−11·86	—
100·94	4·18	7,460	0·02	−0·68	−11·94	—
101·00	4·45	7,540	0·02	−0·70	−11·96	—
101·91	8·48	8,350	0·04	−1·09	−12·35	
101·97	8·74	8,400	0·04	−1·13	−12·39	—
103·5	15·5	9,340	0·08	—	—	—
104·6	20·4	9,980	0·15	—	—	—
106·2	27·6	10,570	0·28	—	—	—
108·0	35·5	11,200	0·60	—	—	—
B. p-*Chloronitrobenzene*, ε_{ion} = 15,900, ε_{base} = 810 *at* λ 3650 A.						
94·8	—	762	—	—	—	—
96·36	—	845	—	—	—	—
98·02	—	910	—	—	—	—
99·04	—	980	—	1·94	− 9·61	−11·57
99·05	—	1,020	—	1·85	− 9·62	−11·47
99·58	—	1,280	—	1·49	− 9·97	−11·46
99·59	—	1,280	—	1·49	− 9·99	−11·48
99·99	—	3,570	—	0·65	−10·87	−11·52
100·06	—	5,970	—	0·28	−11·18	−11·46
100·07	—	6,090	—	0·27	−11·19	−11·46
100·47	—	9,570	—	−0·14	−11·66	−11·52
100·48	—	9,640	—	−0·15	−11·66	−11·51
						−11·49 ± 0·03
100·50	2·22	9,860	—	−0·18	−11·67	—
101·11	4·93	12,040	—	−0·46	−11·95	—
101·48	6·57	12,910	—	−0·61	−12·10	—
101·49	6·61	13,120	—	−0·65	−12·14	—
102·26	10·0	14,180	—	−0·89	−12·38	—
102·68	11·9	14,490	—	−0·99	−12·48	—
103·30	14·6	15,080	—	−1·24	−12·73	—
103·55	15·8	15,250	—	−1·35	−12·84	—
103·89	17·3	15,520	—	—	—	—
105·74	25·5	15,890	—	—	—	—
107·7	34·2	15,890	—	—	—	—
C. p-*Nitrotoluene*, ε_{ion} = 18,000, ε_{base} = 1850 *at* λ 3650 A.						
95·30	—	2,370	—	1·48	− 8·79	−10·27
98·73	—	4,280	—	0·75	− 9·50	−10·25
98·91	—	4,500	—	0·71	− 9·56	−10·27
99·07	—	4,780	—	0·65	− 9·64	−10·29
100·50	2·22	17,320	0·11	−1·36	−11·64	−10·31
100·92	4·08	17,890	0·26	—	—	—
						−10·28 ± 0·02

* Values of the acidity function of media for which % H_2SO_4 $\nless$100·0 are taken from the Tables of Hammett and others (*loc. cit.*).

of charge by conjugation or hyperconjugation between the *p*-chloro- or *p*-methyl substituent and the point of attachment of the proton is comparatively great, certainly greater than in the corresponding isoelectronic *p*-substituted benzoate ions (which, however, are anion bases). Additional evidence on this point will be considered in the following paper. Similar effects are observed in the series of *p*-substituted acetophenones (Flexser and Hammett, *J. Amer. Chem. Soc.*, 1938, **60**, 885).

EXPERIMENTAL.

Materials.—*p*-Nitrotoluene, f. p. 51·5°, was purified by several recrystallisations from alcohol and from light petroleum. *p*-Chloronitrobenzene, m. p. 83°, was obtained in white crystals by recrystallisation from light petroleum and then successively from 50% nitric acid and aqueous alcohol. Nitrobenzene, f. p. 5·72°, was prepared from purified benzene, f. p. 5·5°, according to the directions of Masson (*Nature*, 1931, **128**, 726).

Fuming sulphuric acid was prepared by distillation of sulphur trioxide from commercial oleum containing potassium persulphate into concentrated sulphuric acid in an all-glass apparatus. Sulphur dioxide was oxidised by the persulphate if the strength of the oleum did not exceed about 30% of SO_3. The storage and analysis of the acids have been described previously (Brand, *J.*, 1946, 585). At wave-lengths exceeding about 2500 A. the media were sufficiently transparent to be used in thicknesses up to 10 cm.

Measurement of Extinction Coefficients.—The extinction coefficients were determined qualitatively throughout the near ultra-violet region by use of a Hilger Spekker photometer and a medium quartz spectrograph, and were evaluated by the usual equation, $\log I_0/I = \varepsilon.c.d$, where c is the concentration of solute in moles per litre and d is the thickness, in cm., of the absorbing layer. The changes in the spectrum which accompany ionisation are shown in Figs. 1—3. More accurate values of ε ($\pm 1\%$) were measured at λ 3650—3663 A. with a photoelectric apparatus, and the results are collected in Tables I and II, and Fig. 4.

TABLE II.

Influence of hydrogen sulphates on the acidity function of oleum.

Medium.		Added salt.				
% H_2SO_4.	$[SO_3]$ concn., mol./kg.		concn., equiv./kg.	Extinction coefficient, ε.	log [B]/[BH⁺].	Acidity function, H_0.
A. *Nitrobenzene indicator*, $\varepsilon_{ion} = 9000$, $\varepsilon_{base} = 300$ *at* λ 3650 A.						
100·46	0·26	—	—	6530 *	−0·40	−11·66
100·457	0·254	$Ba(SO_4Me)_2$	0·0830	4950	−0·06	−11·32
100·443	0·247	K_2SO_4	0·0977	4380	0·05	−11·21
100·456	0·253	K_2SO_4	0·146	3530	0·23	−11·03
100·444	0·247	$Ba(SO_4Me)_2$	0·183	2790	0·40	−10·86
100·463	0·258	K_2SO_4	0·198	2760	0·41	−10·85
100·455	0·253	K_2SO_4	0·253	1980	0·62	−10·64
100·87	0·48	—	—	7250 *	−0·60	−11·86
100·858	0·477	$Ba(SO_4Me)_2$	0·102	6180	−0·32	−11·58
100·874	0·486	K_2SO_4	0·150	5300	−0·13	−11·39
100·852	0·473	$Ba(SO_4Me)_2$	0·197	4770	−0·03	−11·29
100·844	0·469	$BaSO_4$	0·216	4820	−0·04	−11·30
100·862	0·479	K_2SO_4	0·257	3820	0·08	−11·18
100·840	0·465	K_2SO_4	0·364	2440	0·49	−10·77
100·838	0·466	K_2SO_4	0·576	1150	0·97	−10·29
B. p-*Chloronitrobenzene indicator*, $\varepsilon_{ion} = 15{,}900$, $\varepsilon_{base} = 810$ *at* λ 3650 A.						
102·68	1·49	—	—	14,490 *	−0·99	−12·48
102·57	1·43	K_2SO_4	0·0494	14,090	−0·87	−12·36
102·55	1·42	K_2SO_4	0·145	13,050	−0·63	−12·12
102·53	1·41	K_2SO_4	0·169	12,390	−0·52	−12·01
102·52	1·40	K_2SO_4	0·244	11,380	−0·37	−11·86
102·51	1·39	K_2SO_4	0·247	11,350	−0·37	−11·86
103·55	1·97	—	—	15,250 *	−1·35	−12·84
103·52	1·95	K_2SO_4	0·0988	14,560	−1·01	−12·50
103·47	1·93	K_2SO_4	0·249	13,270	−0·67	−12·16
103·39	1·89	K_2SO_4	0·488	10,460	−0·25	−11·74
103·33	1·85	K_2SO_4	0·608	8,960	−0·07	−11·56
104·44	2·47	K_2SO_4	0·246	14,440	−0·97	−12·46
104·44	2·47	K_2SO_4	0·246	14,490	−0·99	−12·48
104·35	2·42	K_2SO_4	0·479	12,510	−0·54	−12·03
104·34	2·41	K_2SO_4	0·501	11,440	−0·50	−11·99

* Table I, average.

The calibration of the apparatus was checked by using an alkaline solution of potassium chromate (von Halban, *Z. physikal. Chem.*, 1922, **100**, 221).

Calculation of Ionisation Constants and Acidity Function.—The ionisation ratio of each base in a particular medium was calculated from the photoelectric results. Independently of the changes due to ionisation, the spectra moved gradually towards longer wave-lengths as the strength of the sulphuric acid medium was increased, and in order that this effect should not unduly affect the evaluation of the ionisation ratio, values of ε_{ion} and $\varepsilon_{\text{base}}$ were chosen as close as possible to the steep portions of the curves in Fig. 4. To assist in this, the complete spectra were used to determine the range of composition of the medium within which ionisation took place. The ionisation constants were obtained from the values of the ionisation ratio of the indicators in concentrated sulphuric acid, by use of the established acidity scale, and the acidity function hence extended into fuming sulphuric acid containing up to 14% of free sulphur trioxide (Tables I and V). Table II contains measurements of the acidity function of fuming sulphuric acid in the presence of potassium sulphate, barium sulphate, and barium di(methyl sulphate).

The ionisation constant of *p*-nitrotoluene was also calculated at regular intervals of frequency from the extinction coefficients obtained from the spectra in Fig. 1 (Table III). The method of calculation is described by Flexser, Hammett, and Dingwall (*J. Amer. Chem. Soc.*, 1935, **57**, 2103). The spectrum of the ion of *p*-nitrotoluene, which was not measured because of sulphonation, has been calculated from the other curves.

p-Nitrotoluene and nitrobenzene reacted with fuming sulphuric acid and the transmission was extrapolated back to zero time. The rate of diminution of the intensity of absorption is recorded in Table I. *p*-Chloronitrobenzene was not attacked.

TABLE III.

Calculation of the ionisation constant of p-*nitrotoluene from the absorption spectrum,* λ 2500—4500 A.

		Extinction coefficients.								
Frequency,	% H_2SO_4:	85·6	95·86	99·08	99·15	99·36	99·70	100·00	ε_{ion}	
cm.$^{-1}$.	H_0:	−7·9	−8·93	−9·64	−9·67	−9·80	−10·11	−10·89	(calc.).	−pK_a.
22,000		0	0	68	74	85	108	269	340	10·16
23,000		0	66	296	296	390	603	1,250	1,560	10·28
24,000		10	260	950	970	1170	1900	4,200	5,250	10·22
25,000		87	670	2250	2480	3030	4570	9,820	12,270	10·22
26,000		480	1350	4170	3890	5300	7240	14,100	17,500	10·17
27,000		1500	2360	4950	4530	6320	7820	14,100	17,300	10·13
28,000		3300	3700	5510	5380	6320	7050	10,750	12,620	10·14
29,000		5800	—	6310	6310	6460	6610	7,460	7,860	10·11
30,000		8470	—	7500	7500	7280	6920	5,180	4,350	10·10
31,000		9820	—	8510	8320	7800	7360	3,810	3,200	10·23
32,000		9890	9590	8810	8570	7850	7410	3,080	1,370	10·34
33,000		9200	8850	8130	7930	7400	6930	2,630	980	10·25
34,000		7380	7140	6700	6670	6280	5330	2,010	660	10·34
35,000		5510	5190	4980	4960	4700	3780	1,380	340	9·87
36,000		3980	—	3390	3340	3150	2510	990	260	10·45
37,000		2630	—	2190	2090	1960	1650	720	240	10·20
38,000		1800	—	1380	1310	1290	1170	600	300	9·90
39,000		1340	—	1050	1000	1010	950	650	480	9·73

Average pK_a − 10·19 ± 0·1

DISCUSSION.

The acidity function of anhydrous sulphuric acid was found by Hammett and Deyrup (*loc. cit.*) to be −10·60 units. According to the results of a revised determination of the strengths of some of the more basic indicators by Hammett and Paul (*loc. cit.*) and by Braude (*J.*, 1948, 1976) the original scale should be corrected by subtracting 0·29 unit or 0·45 unit respectively. The method of Hammett and his co-workers was modified and improved by Braude, but in this paper the value adopted provisionally is −10·89, being obtained from measurements of the same type throughout.

The acidity function of 87—100% sulphuric acid may be calculated from the molecular composition, apart from a constant term. The ionisation ratio of an uncharged basic indicator is governed by the equilibrium

$$B + H_2SO_4 \overset{K}{\rightleftharpoons} BH^+ + SO_4H^- \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

and, therefore, $(B)/(BH^+) = (SO_4H^-)/K(H_2SO_4)$, where parentheses refer to activities. This equation may be combined with equation (1) to give equation (3):

$$H_0 = pK_a + pK + \log\,[SO_4H^-]/[H_2SO_4] + \log\{f_{BH^+} \,.\, f_{SO_4H^-}/f_B \,.\, f_{H_2SO_4}\} \quad . \; . \; . \quad (3)$$

To quite a good approximation, water and molecular sulphuric acid react quantitatively to give oxonium and bisulphate ions. In mixtures in which sulphuric acid is present in molecular excess over water, the molar ratio SO_4H^-/H_2SO_4 can, therefore, be calculated directly from the composition of the medium, and in Table IV the acidity function is evaluated in this way from the semi-theoretical equation (4):

$$H_0 = -8{\cdot}35 + \log [SO_4H^-]/[H_2SO_4] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

the constant term being obtained empirically. The agreement is poor at the top of Table IV owing to self-ionisation of the sulphuric acid, and the calculation cannot be extended to more aqueous acid because it is then certainly incorrect to assume that water is converted quantitatively into oxonium ions. The results for media between 87% and 99·8% sulphuric acid are satisfactory, however, in spite of the fact that the activity coefficients do not enter symmetrically into the final term in equation (3) which was disregarded in writing equation (4). The constancy of this term would imply that the ion-activity coefficients are practically constant throughout the range of medium composition under discussion, and this conclusion is difficult to justify, although the deviations would be on a reduced scale in a solvent of high dielectric constant. It is possible that the effect of neglecting the activity-coefficient term is fortuitously compensated by a small reversibility of the reaction between water and molecular sulphuric acid (cf. Ingold and others, *Nature*, 1946, **158**, 480), because the assumption that these components of the system react together *quantitatively* exaggerates the acidity of sulphuric acid and should, of itself, yield results more negative than those observed experimentally. Since the ionic activity coefficients would (initially) decrease from unity, the logarithm of their product would be negative and the approximation involved in writing equations (3) and (4) partly cancel one another. Nevertheless, the diminishing concentration of bisulphate ions in acids containing a small proportion of water (0·5—0·0% of H_2O) obviously accounts for the sharp rise of the acidity function in this region (cf. Lewis and Bigeleisen, *J. Amer. Chem. Soc.*, 1943, **65**, 1144).

TABLE IV.

Comparison of calculated and observed values of the acidity function (87·5—100% H_2SO_4).

Medium.		Molar ratio,	Acidity function.	
% H_2SO_4.	% H_2O.	SO_4H^-/H_2SO_4.	Calc.	Obs.*
99·9	0·1	0·0055	−10·61	−10·49
99·8	0·2	0·0110	−10·31	−10·24
99·5	0·5	0·0282	− 9·90	− 9·91
99·0	1·0	0·0581	− 9·59	− 9·61
98·0	2·0	0·125	− 9·25	− 9·26
96·0	4·0	0·293	− 8·88	− 8·89
95·0	5·0	0·402	(− 8·75)	(−8·75)
94·0	6·0	0·532	− 8·62	− 8·63
92·0	8·0	0·897	− 8·40	− 8·40
90·0	10·0	1·53	− 8·18	− 8·19
87·5	12·5	3·48	− 7·81	− 7·91

* Hammett and others (*loc. cit.*): the calculation uses the experimental value for the acidity function of 95% sulphuric acid.

The Acidity Function of Oleum.—Values of the acidity function of fuming sulphuric acid containing between 0% and 14% of free sulphur trioxide (*i.e.*, sulphur trioxide in excess of the composition H_2SO_4) are collected in Table V.

TABLE V.

Acidity function of fuming sulphuric acid.

SO_3, %	0·0	2·0	4·0	6·0	8·0	10·0	12·0	14·0
H_2SO_4, %	100·0	100·45	100·90	101·35	101·80	102·25	102·70	103·15
$-H_0$	10·89	11·65	11·89	12·06	12·22	12·37	12·53	12·68

Equations (5) and (6) represent alternative possibilities for the equilibrium between the indicator and the medium, the former being analogous to the equilibrium (2):

$$ArNO_2 + H_2S_2O_7 \rightleftharpoons ArNO_2H^+ + S_2O_7H^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$ArNO_2 + SO_3 \rightleftharpoons ArNO_2{\cdot}SO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The ultra-violet spectra do not distinguish between the equilibria (5) and (6), but the question can be decided from the influence of bisulphate ions, added initially to the medium, on the position of the indicator equilibrium. The addition of bisulphate ions establishes a further equilibrium, the position of which lies essentially on the right hand side of equation (7):

$$SO_4H^- + H_2S_2O_7 \rightleftharpoons H_2SO_4 + S_2O_7H^- \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (7)$$

Bisulphate ions, therefore, displace the indicator equilibrium (5) or (6) towards the left by the removal of pyrosulphuric acid (or " free " sulphur trioxide) by the reaction (7). If the indicator is engaged in the equilibrium (5) its ionisation will also be reduced by the mass-action effect of the $S_2O_7H^-$ ions produced in (7), but, on the other hand, if the equilibrium (6) is established, the indicator ionisation ratio will be comparatively insensitive to the presence of $S_2O_7H^-$ ions. The point can be tested by comparing the effects produced on the ionisation ratio of a suitable base by the addition of an equal molal concentration of water and of bisulphate ions. Water reacts quantitatively according to the equation $H_2O + H_2S_2O_7 = 2H_2SO_4$; bisulphate ions also remove pyrosulphuric acid, forming $S_2O_7H^-$ ions according to equation (7). If the indicator is involved in the equilibrium (6), the influences of water and of bisulphate ions on the indicator ionisation ratio should be similar, but if (5) is correct the effect of the bisulphate ions should exceed that of water.

The necessary comparison can be made from the results in Tables I and II, and the figures below show that the influence of potassium bisulphate on the ionisation ratio of *p*-chloronitrobenzene so far exceeds that of water as to leave no doubt that the mass-action effect of the $S_2O_7H^-$ ions on the indicator equilibrium is real. The equilibrium (5) is, therefore, established in the media under discussion, although the possibility remains that (6) may operate in very strong oleum.

Influence of water and potassium hydrogen sulphate on the ionisation ratio of p-*chloronitrobenzene* (medium: 103·55% H_2SO_4).

Added substance.			Added substance.		
	Concn., mol./kg.	log [B]/[BH⁺].		Concn., mol./kg.	log [B]/[BH⁺].
$KHSO_4$	0·00	−1·35	H_2O	0·00	−1·25
„	0·10	−1·01	„	0·10	−1·26
„	0·25	−0·67	„	0·25	−1·14
„	0·49	−0·25	„	0·49	−0·93
„	0·61	−0·07	„	0·61	−0·88

Some measurements of the degree of ionisation of 4 : 5-dibromo-2 : 7-dinitrofluorescein in weak oleum have been reported by Lewis and Bigeleisen (*loc. cit.*), but this compound is a cation base in such media and the related acidity function is H_+ and not H_0. These authors assumed that the equilibrium (6) was established between the indicator and the medium in all fuming acids, and calculated the acidity function of oleum from the partial vapour pressure of sulphur trioxide by the equation: $H = \text{a constant} + \log p_{SO_3}$. The results (cf. Deane, *J. Amer. Chem. Soc.*, 1945, **67**, 329) are quite different from those reported in this paper. It has been claimed (Deane, *loc. cit.*) that the values obtained by Lewis and Bigeleisen are consistent with measurements of the rate of cyclisation of *o*-benzoylbenzoic acid, but the test is inconclusive because the acid does not ionise as a simple base in sulphuric acid solution (Newman, Kuivila, and Garrett, *J. Amer. Chem. Soc.*, 1945, **67**, 704).

UNIVERSITY OF LONDON, KING'S COLLEGE, STRAND, LONDON, W.C.2.
THE UNIVERSITY, GLASGOW, W.2.
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207. *Aromatic Sulphonation. Part II. Kinetics of Sulphonation in Fuming Sulphuric Acid.*

By J. C. D. Brand.

The kinetics of sulphonation of *p*-tolyltrimethylammonium methyl sulphate, phenyltrimethylammonium methyl sulphate, *p*-nitrotoluene, and nitrobenzene have been measured between 0° and 45° in oleum containing up to 33% of sulphur trioxide. The effect of varying initial concentrations and the retarding influence of potassium sulphate, barium sulphate, and barium di(methyl sulphate) have been studied. The experiments were conducted with an excess of sulphur trioxide and were of the first order with respect to the concentration of organic reactant, $-d[\text{ArH}]/dt = k_1[\text{ArH}]$. *p*-Nitrotoluene and nitrobenzene were present in the medium chiefly in a totally unreactive ionised form, and sulphonation occurred through the small equilibrium proportion of un-ionised base. For the quaternary ammonium methyl sulphates and for un-ionised *p*-nitrotoluene and nitrobenzene the variation of k_1 with the composition of the medium is expressed by the equation $\log k_1 = \log A + 2{\cdot}3 \log R$, where A is a parameter characteristic of the substance undergoing suphation and R is the stoicheiometric molar ratio $H_2S_2O_7 : H_2SO_4$. The constants of the Arrhenius equation have been evaluated.

The kinetics are shown to be consistent with the assumption that the governing step in sulphonation is: $SO_3H^+ + \text{ArH} = \text{Ar}{\cdot}SO_3H + H^+$. Relative values of the velocity coefficient of this reaction have been determined.

With emphasis on the theory of reaction kinetics, Hinshelwood and his collaborators (*J.*, 1939, 1372; 1944, 469, 649; 1948, 1065) have studied the kinetics of sulphonation of several aromatic compounds by solutions in nitrobenzene of both sulphuric acid and sulphur trioxide. In this solvent the velocity of sulphonation by sulphur trioxide was of the second order with respect to sulphur trioxide and the reaction was retarded by the product; this was shown to be accounted for if the governing step involved S_2O_6 molecules:

$$2SO_3 \rightleftharpoons S_2O_6;\ S_2O_6 + \text{ArH} = \text{ArS}_2O_6H;\ \text{ArS}_2O_6H \rightleftharpoons \text{ArSO}_3H + SO_3.$$

The kinetics of sulphonation by sulphuric acid in nitrobenzene were consistent with a reversible mechanism involving attack by SO_3H^+ ions and represented by the equilibria

$$2H_2SO_4 \rightleftharpoons SO_3H^+ + SO_4H^- + H_2O$$
$$\text{PhNO}_2 + \text{ArH} + SO_3H^+ \rightleftharpoons \text{PhNO}_2H^+ + \text{ArSO}_3H$$

Sulphonation in Fuming Sulphuric Acid.—Little attention has been paid to the quantitative side of this reaction. The kinetics are quite different from those encountered with nitrobenzene as a solvent: the reaction is more vigorous and is usually not reversible, in the sense that the forward and reverse reactions do not occur under the same conditions. Lauer and others (*J. pr. Chem.*, 1935, **144**, 32; *Ber.*, 1936, **69**, 2618; 1937, **70**, 333) investigated the sulphonation of anthraquinone in oleum but, by varying the concentrations of both reactants simultaneously, obtained a very complicated result which will be discussed later (§ 3). Lauer concluded that molecular (undissociated) sulphuric acid acted as the sulphonating agent both in concentrated and in fuming media, and that sulphur trioxide facilitated the reaction only through its ability to combine with the eliminated water molecule. The kinetics of sulphonation of *p*-nitrotoluene were examined by Martinsen (*Z. physikal. Chem.*, 1908, **62**, 713) in oleum containing 2·4% of sulphur trioxide and by Cowdrey and Davies (*J.*, 1949, 1871) in media containing 1—5·5% of sulphur trioxide. Martinsen also experimented in anhydrous sulphuric acid, and both authors made measurements in acids containing a small proportion of water. In weak oleum, Cowdrey and Davies found that the rate of reaction was given by the differential equation:

$$-d[C_7H_7{\cdot}NO_2]/dt = k_2[C_7H_7{\cdot}NO_2][SO_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[SO_3]$ represents the stoicheiometric concentration of free sulphur trioxide. Martinsen's results also conform to equation (1) (Joffe, *J. Gen. Chem. Russia*, 1933, **3**, 437, 505; *Abstr.*, 1934, 178) and a comparison of some of the published results with those reported in this paper is given in Table IV. However, because of a complicating ionisation of the *p*-nitrotoluene (Part I), these kinetics are not altogether typical of sulphonation. In the following discussion, the kinetics of the most general case will be presented in § 1, and the nature of the changes introduced when the organic reactant is involved in a simultaneous ionisation will be reviewed in §§ 2 and 3.

1. *Kinetics of Sulphonation of Phenyltrimethylammonium and* p-*Tolylmethylammonium Salts.*—In the kinetic experiments the quaternary ammonium salts were introduced as their methyl sulphates, and the progress of the reaction was followed by a modification of Martinsen's

method. The *p*-tolyltrimethylammonium ion reacted exclusively in the *m*-position with respect to the trimethylammonium group, but the phenyltrimethylammonium ion yielded approximately 78% of phenyltrimethylammonium 3-sulphonate, *m*-$Me_3N^+\cdot C_6H_4\cdot SO_3^-$, together with 22% of the *o*- and *p*-isomers (Brand and Rutherford, *Research*, 1949, **2**, 195). The details of the analysis of the products will be published shortly. Because the initial concentration of the quaternary ion was low, the concentration of sulphur trioxide did not change significantly during reaction and individual experiments obeyed equation (2):

$$-d[ArNMe_3^+]/dt = k_1[ArNMe_3^+] \qquad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

The results of a typical experiment are given below.

Expt. 120.

Temp., 25°. Medium, 15·74% of SO_3.

$[SO_3]\begin{cases}\text{initial: } 1{\cdot}968 \text{ mols./kg.}\\ \text{final: } 1{\cdot}923 \text{ mols./kg. (calc.: } 1{\cdot}937 \text{ mols./kg.).}\end{cases}$

Time, mins.	Concn. of $PhNMe_3^+ SO_4Me^-$, mol./kg.	Total reaction, %.	10^3k_1, min.$^{-1}$.
0·0	0·0312	0	—
2·8	0·0280	10·4	39·5
5·7	0·0247	20·9	41·2
9·6	0·0211	32·5	40·8
13·6	0·0177	43·5	41·6
18·7	0·0144	53·9	41·5
24·6	0·0112	64·1	41·6
			41·0 ± 0·6

The results of all velocity measurements are collected in Tables I—VII. Concentrations are expressed in moles per kg. of solution and the time is in minutes. For a given temperature the results may be summarised as follows.

(a) *Influence of composition of medium.* The rate of reaction is a function of the free sulphur trioxide concentration raised to a high and variable power. The reaction order with respect to the molar concentration rises from 2·7 in 4—8% oleum to 4·6 in 16—20% oleum, and a relation of the form $k_1 \propto [SO_3]^n$ applies only if n is expressed as a function of the composition of the medium. A satisfactory empirical correlation exists between k_1 and the molar ratio $H_2S_2O_7 : H_2SO_4$ of the form

$$\log k_1 = \log A + 2{\cdot}3 \log([H_2S_2O_7]/[H_2SO_4]) \qquad . \; . \; . \; . \; . \; . \; . \quad (3)$$

where A is a constant characteristic of the substance undergoing sulphonation (Fig. 1).* The ratio $H_2S_2O_7 : H_2SO_4$ will be written hereafter as R. R is calculated assuming (1) that bisulphate ions react quantitatively according to the equation $SO_3 + SO_4H^- = S_2O_7H^-$, and (2) that the remainder of the free sulphur trioxide is present as molecular pyrosulphuric acid, $H_2S_2O_7$. Methosulphate ($MeSO_4^-$) ions† are counted as bisulphate (SO_4H^-). Assumption (2) is a reasonable first approximation in the moderately dilute oleum under discussion, where the proportion of *molecular* sulphur trioxide is small (Miles, Niblock, and Wilson, *Trans. Faraday Soc.*, 1940, **36**, 345; Miles, Niblock, and Smith, *ibid.*, 1944, **40**, 281); moreover, equation (3) is, for the time being, used quite empirically. The experimental results are given in Table I; values of k_1 are in column 8.

(b) *Influence of basic substances and reactant concentration.* Most inorganic salts are basic towards oleum, and experiments were made to determine the kinetic influence of potassium sulphate, potassium hydrogen sulphate, and barium di(methyl sulphate). These salts retard sulphonation powerfully, and the measured velocities of reaction are given in Table II, column 10. The reaction was also retarded by increasing the concentration of quaternary ammonium ion, but, by simultaneously varying the concentrations of the latter and those of barium di(methyl sulphate) in such a way that the total concentration of methosulphate ions remained constant, it could be shown that the velocity coefficient was approximately independent of the concentration of quaternary ion although very sensitive to alterations in the concentration of methosulphate ions. Equation (2) was, however, essentially valid to cover variations of the initial concentration of quaternary ammonium ion. (This follows, for example, if experiments 97 and 98, Table II, are compared with experiments

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* Equations (3), (5), (7), (8), and (9) were empirically satisfactory in oleum containing 1—33% of sulphur trioxide, but are meaningless if extrapolated to 100% sulphuric acid ($R = 0$) or to very strong oleum.

† Salts containing the grouping $\overset{+}{\gt}$NMe{$MeSO_4^-$ are commonly termed "methosulphates," *e.g.*, pyridine methosulphate. The convenient wording "methosulphate ion" is, however, used to denote $MeSO_4^-$, as this is unlikely to cause confusion. Ed.

TABLE I.

Influence of medium on the rate of sulphonation (*temp.* 25°).

Medium.								
	Sulphur trioxide.							
Acid no.	%.	mol./kg.	log *R*.	H_0.	Expt. no.	Initial concn. of $C_7H_7{\cdot}NMe_3,SO_4Me$.	10^3k_1, min.$^{-1}$.	H_0 + log 10^3k_1 − log *R*.
13	2·44	0·305	−1·54	−11·52	87	0·0330	85	−8·05
13	2·44	0·305	−1·54	—	84	0·0300	86	−8·05
13	2·44	0·305	−1·54	—	83	0·0283	86	−8·05
18	4·10	0·513	−1·28	−11·81	155	0·0308	302	−8·05
18	4·11	0·514	−1·28	—	158	0·0302	303	−8·05
12	7·92	0·990	−0·94	−12·14	82	0·0316	1500	−8·02
12	7·92	0·990	−0·94	—	81	0·0273	1800	−7·94
12	7·94	0·992	−0·94	—	80	0·0252	1800	−7·94
11	11·50	1·439	−0·74	−12·27	78	0·0888	5400	−7·80
						$PhNMe_3,SO_4Me$.		
18	4·08	0·510	−1·28	−11·81	167	0·0301	0·741	−10·66
18	4·10	0·513	−1·28	—	156	0·0304	0·748	−10·66
17	8·23	1·03	−0·92	−12·17	152	0·0301	4·80	−10·57
17	8·23	1·03	−0·92	—	154	0·0300	4·81	−10·57
11	11·60	1·451	−0·72	−12·42	105	0·0296	13·7	−10·56
11	11·60	1·451	−0·72	—	107	0·0302	13·6	−10·57
6	13·04	1·63	−0·66	−12·32	50	0·1036	12·4	−10·57
15	13·39	1·674	−0·64	−12·55	140	0·0304	22·1	−10·57
15	13·40	1·675	−0·64	—	141	0·0299	22·7	−10·55
14	15·74	1·968	−0·53	−12·73	120	0·0312	41·8	−10·58
14	15·74	1·968	−0·53	—	122	0·0297	42·2	−10·57
16	20·12	2·515	−0·35	−13·04	146	0·0300	129	−10·58
16	20·12	2·515	−0·35	—	143	0·0303	127	−10·59
10	24·2	3·02	−0·20	—	73	0·112	240	—
10	24·2	3·02	−0·20	—	74	0·0974	240	—
10	24·2	3·02	−0·20	—	75	0·106	230	—
5	33·1	4·13	+0·20	—	72	0·0964	2000	—

$C_7H_7{\cdot}NMe_3^+$: $\log k_1 = 2{\cdot}3_3 + 2{\cdot}2_3 \log R$. $PhNMe_3^+$: $\log k_1 = -0{\cdot}12 + 2{\cdot}3_6 \log R$.

84, Table I, or 99 and 104 with 101.) Potassium sulphate and barium di(methyl sulphate) exerted roughly the same kinetic effect at the same molar concentration, and the small difference which was observed was probably due to the methyl hydrogen sulphate released in solution from the latter, because the retardation produced by potassium and barium sulphates was indistinguishable (Table VI).

Qualitatively, the retardation by bases is readily interpreted. The effect is caused by the bisulphate ions into which both sulphate and methosulphate ions are converted by the reactions $SO_4^{--} + H_2SO_4 = 2SO_4H^-$ and $SO_4Me^- + H_2SO_4 = MeSO_4H + SO_4H^-$ respectively. The bisulphate ions and molecular pyrosulphuric acid establish the equilibrium

$$SO_4H^- + H_2S_2O_7 = S_2O_7H^- + H_2SO_4 \quad . \; . \; . \; . \; . \; . \; . \; . \quad (4)$$

the position of which lies on the right hand side (Brand, *J.*, 1946, 880). The consumption of pyrosulphuric acid according to equation (4) will diminish the rate of sulphonation, but this effect alone is insufficient to account for the observed retardation, even on the assumption that reaction (4) proceeds quantitatively from left to right. This is illustrated, for example, by the fact that the retardation produced by bisulphate ions is more than twice as great as that brought about by the same number of moles of water. [More exactly, the comparison is between the number of moles of potassium hydrogen sulphate (n_1) and of water (n_2) which produce the same change in *R*, but n_1 and n_2 are approximately equal.] The difference is not a primary salt effect, because no change occurs if the potassium ions are replaced by barium ions, and it is assumed to arise from a mass-action effect of the hydrogen pyrosulphate anions on the equilibria which determine the concentration of the sulphonating agent. The empirical equation (3) does not hold in the presence of added bisulphate ions, unless an additional term is included.

2. *Kinetics of Sulphonation of* p-*Nitrotoluene*.—The velocity of sulphonation of *p*-nitrotoluene was measured by the method referred to in § 1. The experiments yielded first-order rate coefficients (equation 2*a*), except in a limited number of cases in which the concentrations of sulphur trioxide and *p*-nitrotoluene were commensurate and equation (1) was obeyed (Table IV).

$$-[dArNO_2]/dt = k_e[ArNO_2] \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2a$$

TABLE II.

Influence of basic substances and reactant concentration (temp., 25°).

Medium.					Expt.	Initial concn. of	Added substance.			
Acid	Sulphur trioxide.									
no.	%.	mol./kg.	log R.	H_0.*	no.	p-C_7H_7·NMe_3,SO_4Me.		equiv./kg.	10^3k_1.	$H_0 + \log 10^3k_1 - \log R$.
13	2·46	0·307	−1·52	−11·59	86	0·0151	—	—	109	−8·03
		0·307	−1·52	−11·59	85	0·0156	—	—	109	−8·03
		0·305	−1·54	−11·52	Table I	0·030	—	—	86	−8·05
		0·290	−1·64	−11·34	101	0·0744	—	—	49	−8·01
		0·292	−1·66	−11·32	104	0·0304	K_2SO_4	0·0509	47	−7·99
		0·291	−1·75	−11·15	102	0·0300	K_2SO_4	0·0903	30	−7·92
	2·31	0·289	—	—	103	0·0297	K_2SO_4	0·179	15	—
		0·302	−1·55	−11·52	97	0·0150	$Ba(SO_4Me)_2$	0·0147	91	−8·01
		0·300	−1·55	−11·51	98	0·0152	$Ba(SO_4Me)_2$	0·0161	89	−8·01
		0·295	−1·65	−11·33	99	0·0294	$Ba(SO_4Me)_2$	0·0500	55	−7·94
		0·291	−1·77	−11·11	100	0·0286	$Ba(SO_4Me)_2$	0·1007	32	−7·84
						$PhNMe_3,SO_4Me$.				
11	11·60	1·45	−0·72	−12·41	Table I	0·0300	—	—	13·6	−10·55
		1·43	−0·72	−12·31	109	0·0733	—	—	10·0	−10·57
		1·43	−0·74	−12·31	110	0·0747	—	—	10·0	−10·57
		1·44	−0·74	−12·30	111	0·0296	$Ba(SO_4Me)_2$	0·0503	10·8	−10·53
		1·44	−0·74	−12·30	108	0·0292	$Ba(SO_4Me)_2$	0·0496	11·3	−10·51
		1·38	—	—	119	0·0297	$Ba(SO_4Me)_2$	0·248	4·58	—
		1·44	−0·74	−12·30	112	0·0295	K_2SO_4	0·0501	10·2	−10·55
		1·43	−0·75	−12·20	117	0·0303	K_2SO_4	0·0870	8·19	−10·54
		1·43	−0·78	−12·04	116	0·0303	K_2SO_4	0·150	5·85	−10·49
	11·28	1·41	−0·82	−11·80	118	0·0300	K_2SO_4	0·250	3·66	−10·42
14	15·64	1·968	−0·53	−12·73	Table I	0·030	—	—	42·0	−10·57
		1·934	−0·56	−12·43	128	0·0292	$Ba(SO_4Me)_2$	0·100	27·6	−10·43
		1·951	−0·56	−12·43	131	0·0303	K_2SO_4	0·098	25·4	−10·47
		1·925	−0·60	−12·14	135	0·0299	K_2SO_4	0·250	12·1	−10·46
	14·97	1·871	−0·69	−11·69	137	0·0303	K_2SO_4	0·501	4·40	(−10·36)
		1·844	−0·75	—	139	0·0302	K_2SO_4	0·649	2·47	—
		1·942	−0·56	−12·43	134	0·0305	$KHSO_4$	0·100	25·1	−10·47
		1·942	−0·56	−12·43	132	0·0301	$KHSO_4$	0·100	24·5	−10·48
16	20·12	2·515	−0·35	−13·04	Table I	0·0301	—	—	128	−10·58
		2·49	−0·37	−12·75	148	0·0305	K_2SO_4	0·0101	77·0	−10·49
		2·46	−0·41	−12·40	149	0·0302	K_2SO_4	0·246	39·0	−10·40
	19·20	2·40	−0·48	−11·95	151	0·0305	K_2SO_4	0·498	14·2	(−10·32)

* Part I.

(a) *Influence of medium composition.* The variation of the coefficient k_e with the strength of the medium is shown in Table III, column 8. In weak oleum the order of the reaction with respect to the concentration of sulphur trioxide was close to unity (cf. Cowdrey and Davies, *loc. cit.*), but it failed to remain constant, becoming greater in stronger media (Table IV). The results were satisfactorily expressed by the equation:

TABLE III.

Influence of medium on the rate of sulphonation of p-*nitrotoluene* ($pK_a = -10{\cdot}28$).

Medium.								
	Sulphur trioxide.							
Acid no.	%.	mol./kg.	log R.	Expt. no.	Temp.	Initial concn. of p-$C_7H_7{\cdot}NO_2$, mol./kg.	10^3k_e, min.$^{-1}$.	$pK_a + \log 10^3k_e - \log R$.
3	0·75	0·094	−2·17	21	35°	0·0267	2·20	−7·77
3	0·78	0·097	−2·16	20	—	0·0282	2·15	−7·79
1	2·13	0·267	−1·60	10	—	0·0241	7·27	−7·82
1	—	0·270	−1·60	7	—	0·0247	7·18	−7·82
2	7·37	0·921	−0·97	28	—	0·0246	36·5	−7·75
2	—	0·923	−0·97	15	—	0·0242	37·8	−7·73
2	—	0·923	−0·97	14	—	0·0264	37·0	−7·74
4	13·76	1·720	−0·62	32	—	0·0244	107	−7·63
4	—	1·720	−0·62	33	—	0·0248	103	−7·67
2	7·26	0·908	−1·02	22	—	0·1198	34·8	−7·72
2	—	0·911	−1·02	13	—	0·1205	34·3	−7·72
9	7·45	0·931	−1·01	61	—	0·1208	36·2	−7·71
9	—	0·931	−1·01	62	—	0·1216	36·0	−7·71
8	11·35	1·419	−0·76	63	—	0·1191	75·8	−7·64
4	—	1·696	−0·64	35	—	0·1248	102·6	−7·63
4	—	1·696	−0·64	36	—	0·1266	102·8	−7·63
4	—	1·698	−0·64	31	—	0·1203	103·1	−7·63
4	13·61	1·701	−0·64	30	—	0·1211	104·3	−7·62
18	4·11	0·514	−1·28	160	25°	0·0302	5·58	−8·25
18	—	0·516	−1·28	157	—	0·0302	5·50	−8·26
17	8·28	1·035	−0·92	153	—	0·0299	15·6	−8·17
15	13·38	1·672	−0·64	142	—	0·0307	33·4	−8·11
14	—	1·974	−0·53	127	—	0·0322	45·3	−8·09
14	15·8	1·975	−0·53	129	—	0·0296	45·2	−8·09
16	20·2	2·52	−0·35	144	—	0·0308	73	−8·07
16	—	2·52	−0·35	150	—	0·0301	73	−8·07
9	7·45	0·931	−1·01	60	—	0·1196	13·7	−8·13
8	11·35	1·419	−0·76	59	—	0·1163	26·2	−8·10
8	—	1·420	−0·76	58	—	0·1201	26·3	−8·10
11	—	1·437	−0·75	106	—	0·1189	26·0	−8·11
4	—	1·696	−0·64	39	—	0·1181	35·5	−8·09
4	13·6	1·699	−0·64	37	—	0·1180	35·7	−8·09

$$\log k_e = -0{\cdot}74 + 1{\cdot}1_7 \log R \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (5)$$

which resembles equation (3) except that the order of reaction with respect to R is now $1{\cdot}1_7$ (Fig. 1). The reaction was much slower than might have been expected from the results in § 1. For example, in oleum containing 16% of sulphur trioxide, p-nitrotoluene reacted more slowly than the phenyltrimethylammonium ion although in the same medium the p-tolyltrimethylammonium ion reacted too rapidly for measurement. This lack of reactivity was associated with the ability of p-nitrotoluene to ionise as a base in sulphuric acid (equation 6) since the

$$C_7H_7{\cdot}NO_2 + H_2SO_4 \rightleftharpoons C_7H_7{\cdot}NO_2H^+ + SO_4H^- \quad . \; . \; . \; . \; . \; . \; . \quad (6)$$

ionised form would react less readily than the uncharged molecule with an electrophilic reagent. In oleum, the proportion of reactive, un-ionised base is quite small as shown by the figures below (10^{-4}—10^{-5}M-solution):

SO_3, %	0	2	4	6	8	10	12	14	16
Un-ionised p-nitrotoluene, %...	19·7	4·1	2·4	1·7	1·1	0·81	0·56	0·40	0·27

In solutions which are more concentrated with respect to p-nitrotoluene the proportion of the un-ionised form is somewhat greater. Assuming that the ion, $C_7H_7{\cdot}NO_2H^+$, is so unreactive that sulphonation occurs entirely through the small equilibrium proportion of

TABLE IV.

Second-order velocity coefficients of the sulphonation of p-*nitrotoluene* (*temp.* 25°).

Medium. Sulphur trioxide.		Expt. no.	Initial concn. of $C_7H_7{\cdot}NO_2$, mol./l.	10^3k_2, (min. mole/l.)$^{-1}$.	Ref
%.	mol./l.				
2·4	0·56	—	0·20	5·6	1
2·4	0·56	—	0·40	4·8	1
2·18	0·50	4	0·17	4·4	3
2·16	0·50	3	0·26	4·1	3
2·17	0·50	1	0·29	4·0	3
2·14	0·49	5	0·36	3·7	3
4·12	0·96	—	0·05	5·2	3
7·45	1·75	60	0·22	7·3	3
13·3	3·14	46	0·44	11·3	3
0·91	0·21	—	0·20	5·0	2
2·47	0·69	—	0·20	5·2	2
5·47	1·27	—	0·20	5·7	2

References: 1, Martinsen, *loc. cit.* 2, Cowdrey and Davies, *loc. cit.* 3, This paper.
N.B.—In this Table, concentrations are expressed in *moles per litre*.

un-ionised base, the true velocity of reaction, calculated on the concentration of ***un-ionised*** *p*-nitrotoluene, would be obtained by dividing the observed values of k_0 by the proportion of un-ionised molecules. When this is done (Table V and Fig. 1), the corrected coefficients, k_1, show (i) that the order of reaction with respect to R is 2·3, and (ii) that the absolute rate of reaction is similar to that observed for the *p*-tolyltrimethylammonium ion. The empirical equation which fits the results is

$$\log k_1 = 2{\cdot}32 + 2{\cdot}3_2 \log R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The kinetics of sulphonation of the quaternary ammonium ions and of *p*-nitrotoluene are compatible, therefore, if allowance is made for the basic ionisation of the latter.

TABLE V.

Velocity of sulphonation of un-ionised p-*nitrotoluene* (*temp.* 25°) (pK_a = −10·28).

Medium. Sulphur trioxide.				Fraction of un-ionised $C_7H_7{\cdot}NO_2$.	log 10^3k_0.	log 10^3k_1
%.	mol./kg.	log R.	H_0.			
2·14	0·267	−1·56	−11·65	0·0464	0·41	1·74
4·12	0·515	−1·24	−11·89	0·0239	0·74	2·36
7·38	0·922	−0·966	−12·17	0·0127	1·11	3·01
8·24	1·03	−0·906	−12·25	0·0106	1·19	3·16
11·36	1·42	−0·730	−12·48	0·0063	1·42	3·62
13·36	1·67	−0·632	−12·63	0·0045	1·52	3·87
15·76	1·97	−0·527	−12·81	0·0029	1·66	4·19
20·16	2·52	−0·349	−13·12	0·0014	1·86	4·70

(b) *Influence of added bases.* The sulphonation of *p*-nitrotoluene is retarded by increasing the concentration of reactant and by adding potassium sulphate or other bases to the solution (Table VI). Potassium and barium sulphates produce the same retardation at the same molar concentration. The diminution in velocity brought about by increasing the concentration of *p*-nitrotoluene is accounted for by the basicity of the compound, since the same effect is produced by an equivalent of other bases (*e.g.*, experiments 165 and 166, Table VI). The retarding influence of potassium and barium sulphates on the rate of sulphonation is much smaller than was observed with the quaternary ammonium ions, and is accounted for quantitatively by the removal of free sulphur trioxide according to equation (4). This is illustrated by the entries in the final column of Table VI, where it is shown that ($\log k_1 - \log R$) is approximately constant. (The agreement would be improved by introducing the empirical order of 1·17 from equation 5.) The velocity of reaction is, therefore, a function of the medium composition only, and equation (5) is valid in the presence of bases.

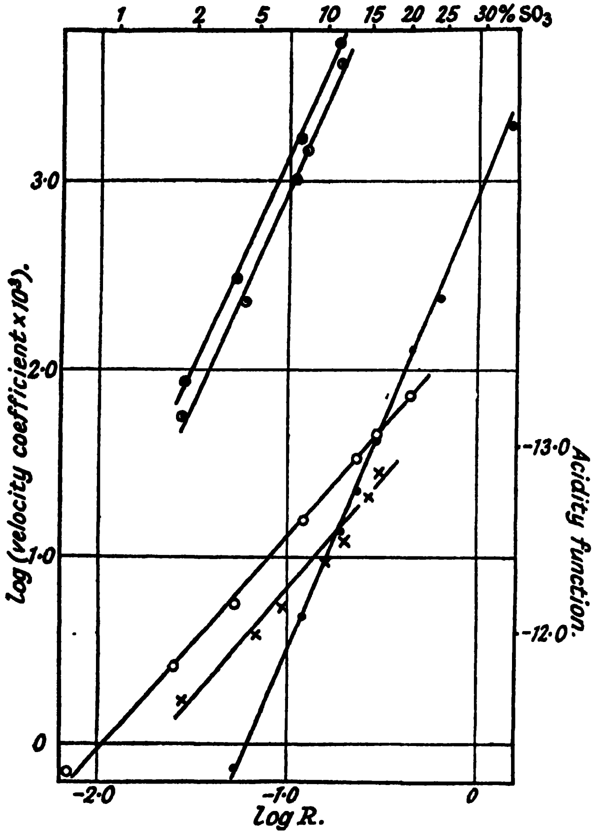
The failure of the hydrogen pyrosulphate ions to retard the reaction is only apparent. It has been shown (Part I) that these ions would displace the equilibrium of *p*-nitrotoluene in favour of the un-ionised form and this effect, which of itself would increase the velocity of reaction, opposes the inherently retarding influence of the $S_2O_7H^-$ ions. The fact that these effects so nearly balance one another is an important clue to the nature of the sulphonating agent, because it demonstrates that the concentrations of un-ionised *p*-nitrotoluene and substituting agent are affected proportionately, but in opposite senses, by a change in the acidity of the medium. With a small qualification, this is precisely the property possessed by two independent acid–base systems ($B_1H^+ \overset{K_1}{\rightleftharpoons} B_1 + H^+$; $B_2H^+ \overset{K_2}{\rightleftharpoons} B_2 + H^+$), it being readily shown that

$$[B_1][B_2H^+]/[B_1H^+][B_2] = K_1/K_2$$

(Square brackets refer to concentrations; the terms involving activity coefficients are symmetrical and have been disregarded.) The analogy with the sulphonation kinetics is demonstrated as follows: let $[B_1]$ represent the fraction of the total concentration of *p*-nitrotoluene present in the un-ionised form, let $[B_2H^+]$ represent the fractional concentration of the sulphonating agent similarly, and assume that the degree of conversion of B_2 into B_2H^+ is small. Then, because both $[B_1]$ and $[B_2H^+]$ are small compared with $[B_1H^+]$ and $[B_2]$ respectively, the rate of sulphonation, which is proportional to the product $[B_1][B_2H^+]$, is seen by rearrangement of the equation above to be constant if the *acidity* of the medium changes, *i.e.* if the total concentrations of $[B_1] + [B_1H^+]$ and $[B_2] + [B_2H^+]$ remain constant. This is the experimental result.

FIG. 1.

Variation of rate coefficients and acidity function with composition of the medium.



⊗ p-$C_7H_7{\cdot}NMe_3^+$ (k_1).
● $NPhMe_3^+$ (k_1).
○ p-$C_7H_7{\cdot}NO_2$ (k_2).
⊙ Un-ionised p-$C_7H_7{\cdot}NO_2$ (k_1).
× Acidity function.

FIG. 2.

Variation of the velocity of sulphonation of nitrobenzene with the composition of the medium.

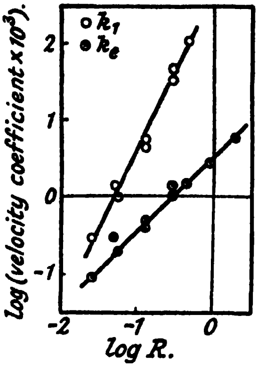


FIG. 3.

Variation of the partial pressure of sulphur trioxide with medium composition.

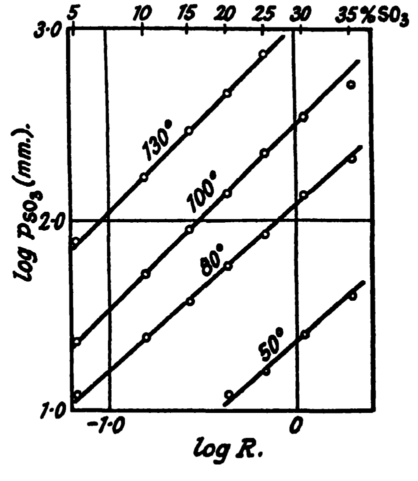


TABLE VI.

Influence of basic substances and reactant concentration upon the velocity of sulphonation of p-*nitrotoluene* (pK_a −10·28).

Medium.							Added substance.			
	Sulphur trioxide.									
Acid no.	%.	mol./kg.	log R.	Temp.	Expt. no.	Initial concn. of p-$C_7H_7{\cdot}NO_2$.		equiv./kg.	10^3k_e, min.$^{-1}$.	$pK_a + \log 10^3k_e - \log R$.
1	2·14	0·268	−1·60	35°	Table III	0·0244	—	—	7·23	−7·82
		0·269	−1·67	—	8	0·0614	—	—	7·0	−7·77
2	7·37	0·922	−0·98	—	Table III	0·025	—	—	37·1	−7·73
		0·915	−1·01	—	12	0·0873	—	—	34·0	−7·74
		0·910	−1·05	—	27	0·0251	K_2SO_4	0·150	32·0	−7·72
		0·898	−1·15	—	26	0·0256	K_2SO_4	0·281	26·0	−7·71
	7·28	0·910	−1·02	—	Table III	0·120	—	—	34·5	−7·72
		0·901	−1·09	—	25	0·119	K_2SO_4	0·098	31·2	−7·70
		0·900	−1·10	—	24	0·114	K_2SO_4	0·126	29·6	−7·71
		0·892	−1·17	—	23	0·119	K_2SO_4	0·217	26·3	−7·69
18	4·12	0·515	−1·28	25°	Table III	0·0304	—	—	5·54	−8·26
		0·508	−1·33	—	166	0·0790	—	—	5·20	−8·23
		0·508	−1·33	—	165	0·0306	$Ba(SO_4Me)_2$	0·0504	5·22	−8·23
4	13·6	1·697	−0·64	—	Table III	0·118	—	—	35·6	−8·08
		1·673	−0·68	—	47	0·120	K_2SO_4	0·1188	32·8	−8·08
		1·668	−0·71	—	40	0·117	K_2SO_4	0·1938	30·2	−8·09
		1·648	−0·76	—	41	0·117	K_2SO_4	0·3168	27·4	−8·09
		1·633	−0·79	—	44	0·117	K_2SO_4	0·3990	25·0	−8·09
		1·661	−0·70	—	42	0·128	$BaSO_4$	0·1644	31·9	−8·08
		1·644	−0·73	—	45	0·118	$BaSO_4$	0·2370	30·0	−8·08
		1·627	−0·77	—	43	0·117	$BaSO_4$	0·3516	25·5	−8·10
14	15·8	1·974	−0·53	—	Table III	0·031	—	—	45·2	−8·09
		1·947	−0·57	—	133	0·0304	K_2SO_4	0·158	41·7	−8·09
		1·921	−0·60	—	136	0·0302	K_2SO_4	0·253	38·0	−8·10
		1·878	−0·68	—	138	0·0308	K_2SO_4	0·498	31·1	−8·11

3. *Kinetics of Sulphonation of Nitrobenzene.*—The velocity of sulphonation of nitrobenzene was measured spectrometrically at 20°. The variation of the experimental coefficient, k_e, with the composition of the medium was similar to that described for *p*-nitrotoluene in § 2 (Fig. 2). The results are expressed by the empirical relation

$$\log k_e = -2{\cdot}4 + 1{\cdot}0 \log R \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (8)$$

The ionisation of nitrobenzene in oleum is extensive, although not so complete as that of *p*-nitrotoluene as the following figures illustrate:

SO_3, %	0	4	8	12	16
Percentage of un-ionised nitrobenzene	70	19	9·9	5·1	2·5

The velocity of sulphonation of un-ionised nitrobenzene can be obtained by the method of § 2*a*, and is given (Fig. 2) by

$$\log k_1 = -0{\cdot}2 + 2{\cdot}3_4 \log R \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (9)$$

Comparing the reactivity of nitrobenzene ($k_{1(a)}$) and the phenyltrimethylammonium ion ($k_{1(b)}$), we obtain from Tables I and VII and equation (9), $k_{1(a)}/k_{1(b)} = 1{\cdot}3$ at 20°. In 87—97% sulphuric acid, where nitrobenzene is un-ionised, the relative rate of nitration is 1·9 at 25° (Bonner, James, Lowen, and Williams, *Nature*, 1949, **163**, 955).

Table VII.

Variation of temperature.

	Medium.					
		Sulphur trioxide.				
Temp.	Acid no.	%.	mol./kg.	Expt. no.	Initial concn. of *p*-C_7H_7·NMe_3,SO_4Me.	$10^3 k_1$ min.$^{-1}$.
14·9°	13	2·44	0·305	91	0·0280	39
14·9	13	2·44	0·305	92	0·0293	41
14·9	13	2·43	0·304	93	0·0307	40
20·0	13	2·44	0·305	94	0·0259	64·3
20·0	13	2·43	0·304	95	0·0314	53·8
20·0	13	2·42	0·303	96	0·0303	62·8
35·0	13	2·44	0·305	88	0·0320	180
35·0	13	2·45	0·306	89	0·0301	210
35·0	13	2·44	0·305	90	0·0277	188
0·0	18	4·09	0·512	161	0·0301	38·9
0·0	18	4·11	0·514	159	0·0303	38·7
					$NPhMe_3$, SO_4Me.	
45·0°	18	4·09	0·512	164	0·0301	4·21
45·0	18	4·07	0·512	163	0·0302	4·26
0·0	11	11·60	1·450	113	0·0292	1·38
40·0	11	11·58	1·448	114	0·0301	45·2
40·0	11	11·61	1·451	115	0·0291	46·8
0·0	14	15·73	1·969	121	0·0290	4·24
0·0	14	15·72	1·968	124	0·0307	4·12
15·4	14	15·73	1·969	126	0·0302	18·4
40·0	14	15·73	1·969	123	0·0301	139·4
40·0	14	15·72	1·968	125	0·0302	140·4
0·0	16	20·1	2·515	147	0·0302	13·1
					p-C_7H_7·NO_2.	$10^3 k_e$.
45·0°	18	4·08	0·514	162	0·0306	44·7
15·0	9	7·45	0·931	66	0·120	4·38
45·0	9	7·45	0·931	65	0·119	115
15·0	8	11·35	1·42	67	0·120	5·81
45·0	8	11·35	1·42	64	0·119	147
0·0	14	15·75	1·97	130	0·0308	2·30
0·0	16	20·2	2·52	145	0·0300	3·82

Note on the Sulphonation of Anthraquinone.—The measurements of Lauer and others (*loc. cit.*) on the velocity of sulphonation of anthraquinone in oleum media were conducted with equal concentrations of anthraquinone and sulphur trioxide. First-order velocity coefficients were obtained which varied in a complicated fashion with reactant concentration. Dilute solutions of anthraquinone in oleum are almost quantitatively converted into the conjugate ion (pK_a = −8·15), but the exceedingly concentrated solutions employed by Lauer contained a kinetically significant proportion of un-ionised anthraquinone, and the interpretation of the results is not straightforward. The view of Lauer and his associates that undissociated sulphuric acid is the effective substituting agent in oleum depended on a mistaken process of correcting the experimental heat of activation by addition of the heat of solution of the product in different oleum media.

4. *Influence of Temperature.*—The variation of the velocity coefficients with temperature for several media may be seen from Table VII, together with results at 25° and 35° from previous tables. For a given medium, log k_1 or log k_e is a linear function of $1/T$. The constants of the Arrhenius equation are assembled in Table VIII. The observation that the apparent heat of activation of *p*-nitrotoluene exceeds that of either of the quaternary ions is an independent argument for the existence of an unreactive form in solution, because in this case the temperature-dependent factor contains a term corresponding to the heat of the reaction represented by equation (10), reading from right to left:

$$p\text{-}C_7H_7\cdot NO_2 + H_2S_2O_7 \rightleftharpoons p\text{-}C_7H_7\cdot NO_2H^+ + S_2O_7H^- \quad . \; . \; . \; . \; . \quad (10)$$

The fact that the pre-exponential factor, A, is close to 10^{11} has been quoted elsewhere as evidence of a bimolecular reaction, but is misleading.

Within the error of measurement, the relative rate of sulphonation of the *p*-tolyl- and phenyl-trimethylammonium ions is accounted for by the difference in activation energies. The activation energies themselves are probably composite quantities.

TABLE VIII.

Constants of the equation, $k_1 = A.e^{-E/RT}$*.

Sulphur trioxide.		$NPhMe_3,SO_4Me$.		$p\text{-}C_7H_7\cdot NMe_3,SO_4Me$.		$p\text{-}C_7H_7\cdot NO_2$.	
%.	concn. mol./kg.	*E*.	log *A*.	*E*.	log *A*.	*E*.†	log *A*.
2·13	0·267	—	—	—	—	19·9	10·23
2·44	0·305	—	—	13·5	7·07	—	—
4·10	0·513	16·3	7·05	13·2	7·42	19·6	10·32
7·45	0·931	—	—	—	—	19·7	10·75
11·35	1·42	—	—	—	—	19·5	10·91
11·60	1·45	14·9	7·30	—	—	—	—
13·7	1·71	—	—	—	—	19·4	10·99
15·7	1·97	15·0	7·83	—	—	19·3	11·06
20·1	2·52	14·9	8·27	—	—	19·2	11·18
24·2	3·02	15·2	8·72	—	—	—	—

* k_e was used in the case of *p*-nitrotoluene: k_1 and k_e were expressed in *seconds*$^{-1}$ at 25° for the calculation of the pre-exponential factor.

† Cowdrey and Davies (*loc. cit.*) found $E = 18$ kcals.

DISCUSSION.

Interpretation of the kinetics is handicapped by incomplete knowledge of the equilibria prevailing in oleum, and by lack of information concerning the influence of the medium and other dielectric effects. It is possible, however, to account for the foregoing in a self-consistent way by assuming that the sulphonating agent in oleum is the ion SO_3H^+, and that substitution occurs according to the equation:

$$SO_3H^+ + ArH = ArSO_3H + H^+ \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (11)$$

Stubbs, Williams, and Hinshelwood (*loc. cit.*) have previously assumed that the reactive ion SO_3H^+ is formed in solutions of sulphuric acid in nitrobenzene.

Variation of the Rate of Sulphonation with Composition of the Medium.—If the velocity coefficient of equation (11) is denoted by k, the equation for the rate of sulphonation takes the form

$$-d[ArH]/dt = k[ArH][SO_3H^+] \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (12)$$

Experimentally, equation (2) applies to a particular set of initial concentrations in a given medium. By combining it with equation (12) we obtain

$$\log k_1 = \log k + \log [SO_3H^+] \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (13)$$

Equation (13) should describe the variation of k_1 with change of medium (apart from purely physical changes), change of reactant concentration, or any other condition except change of temperature. Assuming that *molecular* sulphur trioxide (SO_3) and the SO_3H^+ ion can be treated as a normal acid–base pair, their concentrations will be related to the acidity function of the medium by equation (14), where K_A is the acidic ionisation constant of the ion SO_3H^+, a quantity of unknown magnitude:

$$H_0 = pK_A + \log [SO_3] - \log [SO_3H^+] \quad \ldots\ldots\ldots \quad (14)$$

The concentration of molecular sulphur trioxide will be italicised to distinguish it from the stoicheiometric concentration of free sulphur trioxide. These quantities are not independent of one another (equilibrium 15), but are altogether different in magnitude.

The concentration of molecular sulphur trioxide is determined by the equilibrium (15), the equilibrium constant, K, of which, expressed in terms of concentrations, is given by $K = [H_2S_2O_7]/[H_2SO_4][\mathit{SO_3}]$.

$$H_2SO_4 + SO_3 \rightleftharpoons H_2S_2O_7 \quad \ldots\ldots\ldots \quad (15)$$

If the dissociation of pyrosulphuric acid, by equilibrium (15) or otherwise, is assumed to be small, the expression for the concentration of molecular sulphur trioxide becomes

$$\log [\mathit{SO_3}] = -\log K + \log R \quad \ldots\ldots\ldots \quad (16)$$

where R is the stoicheiometric molar ratio, $H_2S_2O_7/H_2SO_4$, defined in § 1*a*. Equation (16) may be tested by plotting $\log p_{(SO_3)}$ against $\log R$, where $p_{(SO_3)}$ is the partial pressure of sulphur trioxide in oleum (Fig. 3; data of Miles, Niblock, and Wilson, *loc. cit.*): the relation is linear up to 35% oleum, and the slope is unity at 100° and 0·9 at 50° (at lower temperatures the vapour pressure was insufficient for accurate measurement). This appears to justify the use of equation (16) and, by combination of it with (14), the expression for the concentration of the sulphonating agent becomes

$$\log [SO_3H^+] = (pK + pK_A) + \log R - H_0 \quad \ldots\ldots\ldots \quad (17)$$

Equation (17) can be used to evaluate the relative concentration of SO_3H^+ in different media, and the extent to which it is proportional to the velocity of sulphonation is illustrated in Table IX. Equation (17) may also be simplified by expressing the acidity function as an approximately linear function of $\log R$ (Fig. 1), $H_0 = -13{\cdot}5 - 1{\cdot}2 \log R$. Inserting this result into equation (17) gives: $\log [SO_3H^+] = \text{a constant} + 2{\cdot}2 \log R$, which is an expression of the same form as the empirical equations of § 1—3, and furnishes correctly the order of reaction with respect to R.

TABLE IX.

Relation between the velocity of sulphonation of $NPhMe_3^+$ *and the concentration of* SO_3H^+ *ions.*

(Initial concn. of $NPhMe_3,SO_4Me$: 0·03 mol./kg. Temp., 25°.)

Sulphur trioxide { %	4·09	8·23	11·60	13·4	15·7	20·1
Sulphur trioxide { concn., mol./kg.	0·51	1·03	1·45	1·67	1·97	2·51
Relative concn. of SO_3H^+	0·0069	0·0363	0·102	0·166	0·32	1·0
$10^3 k_1$	0·75	4·8	13·6	22·4	42·0	128
$k_1/[SO_3H^+]$	0·11	0·13	0·13	0·13	0·13	0·13

The complete theoretical expression for the velocity of sulphonation of the quaternary ammonium ions and the un-ionised forms of *p*-nitrotoluene and nitrobenzene is obtained from equations (13) and (17), *viz.*:

$$\log k_1 = \log k + \log R - H_0 + (pK + pK_A) \quad \ldots\ldots\ldots \quad (18)$$

In the case of the nitro-compounds, the experimental coefficients, k_e, are related to the coefficients k_1 of the un-ionised forms by the equation, $k_e = k_1[B]$, [B] representing the fraction of the total concentration of the reactant present in the un-ionised form. In the regions where sulphonation occurs with measurable speed, both *p*-nitrotoluene and nitrobenzene are almost quantitatively ionised and, therefore, $\log [B] \sim pK_a - H_0$ (where pK_a is the acidic ionisation constant of the ionised form), and the expression for the observed velocity of sulphonation is (cf. Table X)

$$\log k_e = \log k - \log R - pK_a + (pK + pK_A) \quad \ldots\ldots\ldots \quad (19)$$

Experimentally, the order of reaction with respect to R were observed to be 1·2 and 1·0 for *p*-nitrotoluene (equation 5) and nitrobenzene (equation 8) respectively. If attention is confined to a small range of composition of the medium, the variation of the sulphuric acid mole fraction may be neglected and, therefore, $[\mathit{SO_3}] \propto [SO_3]$ (cf. equation 16). Introducing this approximation in place of equation (16) yields $k_e \propto [SO_3]$, which by combination with equation (2*a*) gives the empirical equation (1), which is a satisfactory expression in weak oleum over a limited range of medium composition.

TABLE X.

Dependence of the velocity of sulphonation of p-*nitrotoluene on the concentration of molecular sulphur trioxide.*

(Initial concn. of $C_7H_7{\cdot}NO_2$: 0·03 mol./kg. Temp., 25°.)

Sulphur trioxide	%	0·75	4·11	8·28	13·4	15·8	20·2
	concn., mol./kg.	0·094	0·51	1·03	1·67	1·97	2·52
R		0·00676	0·0525	0·120	0·229	0·296	0·45
10^3k_e		0·75	5·58	15·6	33·4	45·3	73
k_e/R		0·11	0·11	0·13	0·15	0·15	0·16

The interpretation of the variation of the velocity of sulphonation with the composition of the medium may be summarised as follows: the substituting agent is assumed to be the ion SO_3H^+, the concentration of which is small compared with that of molecular sulphur trioxide; an increase in the total concentration of sulphur trioxide (all forms) brings about (i) an increase in the concentration of molecular sulphur trioxide, and (ii) an increase of acidity, producing a higher degree of conversion of molecular sulphur trioxide into SO_3H^+ ions. The factors (i) and (ii) co-operate, and contribute almost equally to the overall variation of k_1 with the medium composition. With *p*-nitrotoluene and nitrobenzene, (ii) is compensated by a proportionate diminution in the concentration of un-ionised forms, and the variation is accounted for by changes in the concentration of molecular sulphur trioxide alone.

The Influence of Added Salts.—A preliminary account of this subject was given in § 1*b* and § 2*b*, where it was shown that bisulphate ions retard the reaction (i) by diminishing the concentration of free sulphur trioxide according to equation (4), and (ii) by diminishing the acidity by production of $S_2O_7H^-$ ions; each of these factors lowers the concentration of SO_3H^+ ions (equation 14). For *p*-nitrotoluene and nitrobenzene, the changes in the concentration of the un-ionised forms of the nitro-compounds and in the concentration of SO_3H^+ ions are inversely proportional to one another, and the observed retardation is accounted for entirely by the first of the factors listed above. In the presence of salts giving rise initially to bisulphate ions, the extent to which the velocities of sulphonation of *p*-nitrotoluene and the phenyltrimethylammonium ion are proportional respectively to the concentrations of molecular sulphur trioxide and of SO_3H^+ ions is shown in Table XI.

TABLE XI.

Influence of bisulphate ions on the concentration of molecular sulphur trioxide and on the rate of sulphonation of p-*nitrotoluene.*

(Initial concn. of $C_7H_7{\cdot}NO_2$: 0·12 mol./kg. Temp., 25°.)

Medium.						
Sulphur trioxide.			Added substance.		10^3k_e, min.$^{-1}$.	k_e/R
%.	concn., mol./kg.	R.		concn., equiv./kg.		
13·6	1·697	0·227	—	—	35·6	0·157
—	1·673	0·207	K_2SO_4	0·1188	32·8	0·158
—	1·661	0·200	$BaSO_4$	0·1644	31·9	0·159
—	1·668	0·196	K_2SO_4	0·1938	30·2	0·154
—	1·644	0·187	$BaSO_4$	0·2370	30·0	0·160
—	1·648	0·175	K_2SO_4	0·3168	27·4	0·156
13·0	1·627	0·169	$BaSO_4$	0·3516	25·5	0·151
—	1·633	0·161	K_2SO_4	0·3990	25·0	0·155

Influence of basic anions on the concentration of SO_3H^+ *and on the rate of sulphonation of* $NPhMe_3^+$ (temp., 25°).

Sulphur trioxide.		Added substance.		Initial concn. of $C_7H_7{\cdot}NO_2$, mol./kg.	Relative concn. of SO_3H^+.	10^3k_1.	$k_1/[SO_3H^+]$.
%.	concn., mol./kg.		concn., equiv./kg.				
11·6	1·45	—	—	0·030	1·0	13·6	0·0136
—	1·43	—	—	0·074	0·76	10·0	0·0132
—	1·44	K_2SO_4	0·0501	0·029	0·74	10·2	0·0137
—	1·44	$Ba(SO_4Me)_2$	0·0503	0·030	0·74	10·8	0·0145
—	1·43	K_2SO_4	0·0870	0·030	0·58	8·19	0·0141
11·4	1·43	K_2SO_4	0·150	0·030	0·37	5·8	0·0157

The equations (18) and (19) have been tested comprehensively by tabulating values of $(\log k_1 + H_0 - \log R)$ and $(\log k_e + pK_a - \log R)$ in the final colums of Tables I and II, and

Tables III and VI respectively. Each of these expressions is equal to (log k + a constant), and should, therefore, be constant for a particular aromatic compound at a fixed temperature, in so far as k is itself independent of the composition of the medium. Examination of the Tables shows that the extensive experimental variation of the rate of sulphonation is very largely accounted for by the theoretical equations (18) and (19). The deviations which are observed correspond to a gradual rise of k when the concentration of sulphur trioxide is increased, or in the presence of a large concentration of bisulphate ions. The average results obtained for the relative velocity of substitution according to equation (11) at 25° are :

	Relative velocity coefficient (eqn. 11).
p-$C_7H_7 \cdot NMe_3,SO_4Me$	360
Un-ionised p-$C_7H_7 \cdot NO_2$	290
Un-ionised $PhNO_2$ *	1·5
$NPhMe_3,SO_4Me$	1·0 (overall) 0·8 (*m*-positions)

* Calc. from results at 20°, using $E = 22$ kcals.

The sulphonation of unionised *p*-nitrotoluene occurred more slowly than that of the *p*-tolyltrimethylammonium ion, in spite of the fact that un-ionised nitrobenzene reacted faster than $NPhMe_3^+$. The difference is associated with the large interval between the basic strengths of *p*-nitrotoluene and nitrobenzene (Part I), the withdrawal of electrons from the aromatic nucleus by the nitro-group being quantitatively different in the two cases. The velocity of sulphonation of *p*-nitrotoluene was reduced, apparently, at least one-thousand-fold by the addition of a proton, and no definite kinetic evidence of reactivity on the part of the ionised form was obtained.

The scale of the relative velocities of sulphonation is more condensed than is observed for nitration of the same systems, even after taking account of the fact that the phenyltrimethylammonium ion is not sulphonated exclusively in the *m*-position; these two facts should, indeed, be considered together, for the SO_3H^+ ion, being less powerfully electrophilic, is less susceptible to electrostatic influences than is NO_2^+.

EXPERIMENTAL.

Materials.—Phenyltrimethylammonium methyl sulphate, m. p. 126°, and *p*-tolyltrimethylammonium methyl sulphate, m. p. 144·5°, were obtained from the corresponding tertiary amines and methyl sulphate in acetone. The purification of nitrobenzene and *p*-nitrotoluene was referred to in Part I. AnalaR Potassium sulphate, potassium hydrogen sulphate, and potassium nitrate were used and were dried before use. Pure barium sulphate was prepared by slowly adding 0·1M-barium hydroxide to very dilute (½%) boiling sulphuric acid. Barium di(methyl sulphate) [Found: Ba, 38·2, 38·4. Calc. for $Ba(SO_4Me)_2$: Ba, 38·2%)] was dried *in vacuo* over phosphoric oxide and used freshly prepared. The preparation and analysis of oleum have been described previously (Brand, *J.*, 1946, 585).

Velocity Measurements.—These were made at 15·0°, 20·0°, 25·0°, 35·0°, 40·0°, and 45·0° in a thermostatically controlled water-bath and at 0° in an ice-bath. The compound to undergo sulphonation was added as a solid to the oleum, and the start of the reaction timed from this addition. Tests made to determine whether thermal effects occurred on mixing showed a rise in temperature amounting in unfavourable cases to several tenths of a degree. Precautions were taken to compensate for this.

Sampling and Analysis.—For convenience, the solutions were prepared and analysed by weight. During the reaction, samples of the solution were removed by pipette and delivered into concentrated sulphuric acid containing sufficient water to react with the sulphur trioxide introduced. The method of analysis depended on the fact that the unsulphonated aromatic molecules were sufficiently reactive to be estimated quantitatively by nitration in the presence of the sulphonic acids (Martinsen, *loc. cit.*). This was accomplished by adding a standard solution of potassium nitrate in concentrated sulphuric acid to the "arrested" sample and, after a suitable interval, determining the nitric acid by pententiometric titration with ferrous sulphate (Treadwell and Vontobel, *Helv. Chim. Acta*, 1937, **20**, 573). The concentration of the reactant was calculated from the consumption of nitric acid.

The time required for quantitative nitration ranged from one minute or less for *p*-nitrotoluene to some 20 hours at 25° for phenyltrimethylammonium methyl sulphate. Tests showed that no nitration of *p*-nitrotoluene-*o*-sulphonic acid, *p*-tolyltrimethylammonium-2-sulphonate, 4 : 1 : 2-$Me_3N^+ \cdot C_6H_3Me \cdot SO_3^-$, or phenyltrimethylammonium-3-sulphonate occurred in a corresponding period. The analysis was tested repeatedly; some typical results for *p*-nitrotoluene were :

Wt. taken, g.	0·1126	0·1304	0·0981	0·0677	0·0956	0·0907
Found, g.	0·1134	0·1302	0·0985	0·0668	0·0961	0·0906

(Total weight of 0·5951 g. estimated as 0·5956 g.)

Similar determinations with *p*-tolyltrimethylammonium methyl sulphate (*M*, 261) and phenyltrimethylammonium methyl sulphate (*M*, 247) gave an average molecular weight of 260 and 245, respectively.

Some decomposition occurred during the sulphonation of *p*-nitrotoluene, generating about 10^{-4} mole of sulphur dioxide during complete reaction in the more concentrated media. Although the loss of *p*-nitrotoluene was, therefore, small, appreciable reduction of nitric acid occurred during the analysis by nitration, and a correction applied to allow for this raised the velocity coefficient by 1—2%.

Disappearance of Sulphur Trioxide during Sulphonation.—In a number of kinetic experiments the concentration of sulphur trioxide was determined at the end of reaction. Some typical results are given below for the sulphonation of phenyltrimethylammonium methyl sulphate, and indicate that the amount of moisture absorbed during manipulation is small. Similar results were obtained on using *p*-tolyltrimethylammonium methyl sulphate and *p*-nitrotoluene.

Expt. no. :	105	114	115	109	110	120	123
Initial concn. (M.) of $NPhMe_3,SO_4Me$ ...	0·0296	0·0301	0·0291	0·0733	0·0747	0·0312	0·0301
Sulphur trioxide :							
Initial concn. (M.)	1·451	1·448	1·451	1·434	1·435	1·968	1·969
Final concn. Found (M.)	1·405	1·391	1·432	1·359	1·360	1·923	1·934
Final concn. Calc. (M.)	1·421	1·418	1·422	1·361	1·360	1·937	1·939
Final concn. %	98·9	98·1	100·7	99·9	100·0	99·3	99·7

Measurement of the Velocity of Reaction by Alternative Methods.—(*a*) *Change in light absorption.* The velocity of sulphonation of nitrobenzene was obtained by measurement of the initial rate of change of the extinction coefficient, at λ 3650 A., of the solution in oleum. The initial concentration of nitrobenzene was approximately 10^{-4}M., and the results are shown in Fig. 2. As a test of the method, the velocity of sulphonation of *p*-nitrotoluene was also measured and compared with the value obtained by chemical analysis (Tables III and VII) :

		k_1 (min.$^{-1}$).	
Temp.	Medium, $[SO_3]$, mol./kg.	By light absorption.	By chem. analysis.
18°	0·513	0·00258	0·00251
—	0·280	0·00107	0·00106

(*b*) *Dilatometry.* Some experiments were made with a dilatometer so constructed that the capillary limb formed the stopper of the reaction vessel, but were discontinued. However the results served as a useful check and agreed with those obtained by chemical analysis :

			Initial concn. of		k_e (min.$^{-1}$).	
Expt. no.	Temp.	Medium, $[SO_3]$, mol./kg.		mol./kg.	By dilatometer.	By chem. analysis.
54	25°	1·437	*p*-$C_7H_7{\cdot}NO_2$	0·025	0·025	0·026
57	25	1·436	*p*-$C_7H_7{\cdot}NO_2$	0·026	0·025	0·026
53	25	1·62	*p*-$C_7H_7{\cdot}NO_2$	0·026	0·033	0·031
68	35	1·426	$NPhMe_3,SO_4Me$	0·046	0·029	0·029 *

* The velocity coefficient is k_1 in this experiment.

(*c*) *Analysis of the sulphonic acid formed.* Experiments on the rate of formation of 4-nitrotoluene-2-sulphonic acid were carried out as follows. Samples of the reaction mixture were diluted with water, and the sulphuric acid was removed with barium carbonate; the resulting solution of barium 4-nitrotoluene-2-sulphonate (containing some barium carbonate) was concentrated to a standard volume and the barium determined gravimetrically by precipitation with sulphuric acid The results of two such experiments were :

				k_e (min.$^{-1}$) analysis for	
Expt. no.	Temp.	Medium, $[SO_3]$, mol./kg.	Initial concn. of *p*-$C_7H_7{\cdot}NO_2$, mol./kg.	4-nitrotoluene-2-sulphonic acid.	*p*-nitrotoluene.
70	25°	1·41	0·1212	0·026	0·026
71	25	1·41	0·1214	0·027	

King's College, London.
The University, Glasgow.

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NOTES.

The Chloro- and Iodo-acetates of Dihydrolanosterol and Dihydroagnosterol. By R. G. Curtis.

The *X*-ray examinations of derivatives containing atoms of high atomic weight have given considerable information concerning the arrangement of the rings and side chain in sterols (Crowfoot and Dunitz, *Nature*, 1948, **162**, 608). It is intended to apply this method of structure analysis to some of the wool-wax triterpenes, and for this purpose the iodoacetates of dihydrolanosterol and dihydroagnosterol have been prepared. They were obtained from the corresponding chloroacetates, potassium iodide, and acetone, the chloroacetates being readily prepared from chloroacetic anhydride and the alcohol. Attempts to esterify dihydrolanosterol and dihydroagnosterol with iodoacetyl chloride directly were not successful.

Experimental.—(a) *Dihydrolanosteryl chloroacetate* was prepared by heating dihydrolanosterol (5 g.) with chloroacetic anhydride (15 g.) on a steam-bath (3 hours); water was added, the mixture was warmed to destroy excess of anhydride, and the solid was washed with hot water and recrystallised three times from hot chloroform (20 ml.)–methanol (60 ml.), to give fine white needles (3·6 g.), m. p. 114·5—115°, $[\alpha]_D^{20}$ +57·1° (*c*, 3 in chloroform) (Found: C, 76·2; H, 10·5. $C_{32}H_{53}O_2Cl$ requires C, 76·1; H, 10·6%).

(b) *Dihydroagnosteryl chloroacetate* prepared in like manner from dihydroagnosterol (5 g.) formed prisms (3·4 g.), m. p. 143·5—144°, $[\alpha]_D^{24}$ +89·3° (*c*, 3 in chloroform) (Found: C, 76·4; H, 10·0. $C_{32}H_{51}O_2Cl$ requires C, 76·4; H, 10·2%).

(c) *Dihydrolanosteryl iodoacetate* was prepared by refluxing (3 hours) the chloroacetate (1 g.) in acetone (50 ml.) with potassium iodide (3 g.). After removal of the solvent and thorough washing of the residue with water, three crystallisations from chloroform–methanol (1 : 3; 15 ml.) gave glistening prisms (0·65 g.), m. p. 105—105·5°, $[\alpha]_D^{21}$ +52·9° (*c*, 3 in chloroform) (Found: C, 64·6; H, 8·7; I, 21·3. $C_{32}H_{53}O_2I$ requires C, 64·6; H, 8·95; I, 21·3%).

Dihydrolanosterol, m. p. 142—143°, was obtained by hydrolysis of the iodoacetate with alcoholic potassium hydroxide (4%).

(d) *Dihydroagnosteryl iodoacetate* prepared in like manner from dihydroagnosteryl chloroacetate (1 g.) and thrice crystallised formed glistening plates (0·85 g.), m. p. 114—114·5°, $[\alpha]_D^{23}$ +67·5° (*c*, 3 in chloroform) (Found: C, 64·6; H, 8·6; I, 21·1. $C_{32}H_{51}O_2I$ requires C, 64·6; H, 8·6; I, 21·3%). Dihydroagnosterol, m. p. 154—155°, was obtained by hydrolysis of the iodoacetate with alcoholic potassium hydroxide (4%).

The dihydrolanosterol, m. p. 146—147°, $[\alpha]_D$ +62·8° (*c*, 3 in chloroform), and dihydroagnosterol, m. p. 158—159°, $[\alpha]_D$ +67·5° (*c*, 3 in chloroform), used were prepared according to the methods described by F. J. McGhie ("Contributions to the Chemistry of the Sterols," Thesis, London, 1947).

The author is indebted to H. L. Oates and L. Llewelyn of this laboratory for the microanalyses. This work forms part of the research programme of this Division.—DIVISION OF INDUSTRIAL CHEMISTRY, COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION, AUSTRALIA. [*Received, December 14th*, 1949.]

The Nitration of pp′-*Dichloroazobenzene.* By C. D. HOUGHTON and WILLIAM A. WATERS.

PREVIOUS workers (cf. Burns, McCombie, and Scarborough, *J.*, 1928, 2928) have established that azobenzene and many of its derivatives nitrate and brominate in the *para*-position to the azo-group. Further, the nitrations of both the *o*- and the *m*-methylazobenzenes in the 4- and 4′-positions and the bromination of *m*-methylazobenzene in the 4-position indicate that the azo-group (or possibly the phenylazo taken as a whole) has a greater orienting power than the methyl group. In connection with another investigation (see Ford, Waters, and Young, *J.*, 1950, 833) it was of interest to determine, from the mode of cationoid substitution of *pp*′-dichloroazobenzene, the relative orienting powers of the chloro- and azo-groups, and consequently both the nitration and the bromination of *pp*′-dichloroazobenzene have been examined.

The nitration of *pp*′-dichloroazobenzene with fuming nitric acid in glacial acetic acid solution yields a dichloronitroazoxybenzene, m. p. 134°, which can also be obtained by the direct nitration of *pp*′-dichloroazoxybenzene. Under less drastic conditions nitration of the azo-compound does not occur. The product, m. p. 134°, has previously been obtained from *pp*′-dichloroazoxybenzene by both Calm and Heumann (*Ber.*, 1880, **13**, 1184) and Heumann (*Ber.*, 1872, **5**, 912), but these early investigators did not attempt to determine its exact structure. Calm and Heumann showed that their azoxy-compound could be reduced with cold alcoholic ammonium sulphide to a 4 : 4′-dichloro-nitroazobenzene. We have repeated this work, and have now found that this nitro-compound, on further reduction with tin and hydrochloric acid, yields a mixture of amines from which, by condensation with phenanthraquinone, we have been able to isolate 6-chloro-1 : 2-3 : 4-dibenzphenazine, identical with the product prepared by Ullmann and Mauthner (*Ber.*, 1904, **36**, 4028) from 4-chloro-*o*-phenylenediamine.

The nitration of *pp*′-dichloroazobenzene therefore yields 4 : 4′-dichloro-2-nitroazoxybenzene. Whether the nitration of the azo-compound precedes its oxidation, or the reverse, is as yet undecided, but it is now clear that both the azo- and the azoxy-group have a very marked *ortho-para* orienting power.

We failed to achieve the direct bromination of *pp*′-dichloroazobenzene, but prepared a sample of 4 : *4′-dichloro-2-bromoazobenzene* for reference purposes.

Experimental.—*pp*′-Dichloroazobenzene was prepared by condensing *p*-chloronitrosobenzene with *p*-chloroaniline, whilst *pp*′-dichloroazoxybenzene was obtained as a by-product of the preparation of *p*-chloronitrosobenzene.

4 : *4′-Dichloro-2-nitroazoxybenzene* was obtained by dissolving *pp*′-dichloroazobenzene (3 g.) in a mixture of fuming nitric acid (50 ml.) and glacial acetic acid (20 ml.) at −10°. The mixture was poured into water after keeping it at 0° for 30 minutes, and the solid was collected and crystallised repeatedly from alcohol. It formed fine yellow needles, m. p. 134° (Found: C, 46·6; H, 2·2; N, 13·4. $C_{12}H_7O_3N_3Cl_2$ requires C, 46·5; H, 2·2; N, 13·4%). The same product was obtained by dissolving *pp*′-dichloroazoxybenzene in a similar mixture of nitric and acetic acids.

4 : *4′-Dichloro-2-nitroazobenzene* was prepared by keeping the nitro-azoxy-compound overnight with a mixture of equal volumes of ethyl alcohol and saturated ammonium sulphide solution. The product was precipitated with water, collected, and freed from sulphur by crystallisation from alcohol. It formed deep orange-red needles, m. p. 210° (Found: C, 48·9; H, 2·35; N, 14·2. $C_{12}H_7O_2N_3Cl_2$ requires C, 49·0; H, 2·4; N, 14·2%). An attempt to synthesise this compound by condensing together *p*-chloronitrosobenzene and 4-chloro-2-nitroaniline failed; the nitro-amine could be recovered unchanged after the two substances had been heated under reflux in glacial acetic acid.

4 : 4′-Dichloro-2-nitroazobenzene (5 g.) was reduced by boiling it with granulated tin (5 g.) in alcohol under reflux, and adding, from time to time, small portions (2—3 ml.) of concentrated hydrochloric acid until most of the tin had dissolved. The solution was then filtered from tin, diluted with one quarter of its volume of water, boiled for ½ hour (charcoal), and refiltered. This filtrate was then heated for 10 minutes with an aqueous solution of phenanthraquinone (3·6 g.), sodium acetate (5 g.), and sodium

hydrogen sulphite (5 g.). 6-Chloro-1 : 2-3 : 4-dibenzphenazine gradually separated in filterable form. After crystallisation three times from nitrobenzene–glacial acetic acid (equal volumes) it formed pale yellow-green needles, m. p. 245°, which on sublimation in a vacuum gave white, feathery crystals, m. p. 246° (Found : C, 76·4; N, 8·8; Cl, 11·2. Calc. for $C_{20}H_{11}N_2Cl$: C, 76·4; N, 8·9; Cl, 11·3%). Ullmann and Mauthner (*loc. cit.*) describe this compound as forming pale yellow-green needles, m. p. 246°.

4 : 4′-*Dichloro-2-bromoazobenzene* was obtained by heating 4-chloro-2-bromoaniline (1·2 g.) with *p*-chloronitrosobenzene (0·8 g.) in glacial acetic acid at 100° for 10 minutes. The product crystallised from alcohol in orange-red needles, m. p. 145° (Found : C, 44·0; H, 2·1; N, 8·4. $C_{12}H_7N_2Cl_2Br$ requires C, 43·9; H, 2·2; N, 8·5%).

pp′-Dichloroazobenzene resisted bromination (i) by refluxing with bromine in glacial acetic acid solution in the presence of anhydrous sodium acetate, (ii) by heating for 10 hours at 100° with liquid bromine and a few drops of pyridine, and (iii) by heating at 100° in 90% sulphuric acid in the presence of both bromine and silver sulphate (compare Derbyshire and Waters, *J.*, 1950, 573).—THE DYSON PERRINS LABORATORY, OXFORD. [*Received, December 15th*, 1949.]

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p-*Cymene-2-sulphonamides.* By (MISS) S. M. BROWN and G. H. THOMSON.

DURING the investigation of new surface-active agents, it was found that some amine derivatives of *p*-cymene-2-sulphonyl chloride are more difficult to prepare than the corresponding derivatives from benzene- and toluene-sulphonyl chlorides.

All b. p.s and m. p.s are uncorrected.

Preparation of Pure p-*Cymene.*—Commercial *p*-cymene (1 kg.) was shaken three times with concentrated sulphuric acid (900 c.c. in all); the top layer was washed successively with water, 1% potassium permanganate solution, 2N-potasium carbonate solution, and water again, dried (Na_2SO_4), and distilled; b. p. 175—176°; yield, 510 g.

p-*Cymene-2-sulphonyl Chloride.*—*p*-Cymene (67 g.) at 0° was added dropwise to stirred, ice-cold chlorosulphonic acid (180 c.c.) (B.D.H. techn.), the temperature being kept below 5°. When the addition was complete (90 minutes), the mixture was poured on 2 kg. of crushed ice, and the oily layer separated, washed, dried, and distilled; it had b. p. 163—165°/15 mm.; yield, 75 g. The sulphonamide, m. p. 115° (Found : N, 6·62. Calc. for $C_{10}H_{15}O_2NS$: N, 6·57%), was obtained quantitatively from the chloride, but the overall yield (84—87%) quoted by Huntress and Autenrieth (*J. Amer. Chem. Soc.*, 1941, **63**, 3446) was not attained.

Substituted Amides.—The amine (2 g.) was shaken with 10% sodium hydroxide (20 c.c.), and *p*-cymenesulphonyl chloride (6 g.) added in one-fifth portions; the mixture was shaken for 5 minutes after each addition. After 15 minutes' boiling and 2 hours' storage, a solid product was obtained, which formed white crystals from ethanol: p-*Cymene-2-sulphonanilide* (2-*methyl*-5-iso*propylbenzenesulphonanilide*) had m. p. 132·5° (Found : N, 4·90. $C_{16}H_{19}O_2NS$ requires N, 4·84%); the cyclo*hexylamide* had m. p. 82° (Found : N, 4·74. $C_{16}H_{25}O_2NS$ requires N, 4·71%), and the o-, m-, and p-*toluidine* analogues had m. p. 101°, 101·5°, and 129°, respectively (Found : N, 4·7, 4·7, 4·7, respectively. $C_{17}H_{21}O_2NS$ requires N, 4·6%).

Derivatives from benzidine and 4-*methyl*-1 : 3-*phenylenediamine.* Benzidine (2·3 g.) or 3-methyl-1 : 4-phenylenediamine (1·5 g.) was shaken with 10% sodium hydroxide (40 c.c.), and the sulphonyl chloride (6 g.) added in one-fifth portions, the mixture being boiled after each addition and finally boiled under reflux for 1 hour and then set aside overnight. The *benzidine* analogue of the above formed grey crystals from *n*-butanol, m. p. 257—258° (Found : N, 7·35. $C_{22}H_{24}O_2N_2S$ requires N, 7·37%), and the 4-*methyl*-1 : 3-*phenylenediamine* derivative formed grey crystals from ethanol (Found : N, 9·10. $C_{17}H_{22}O_2N_2S$ requires N, 8·81%), m. p. 166°. In neither case did further treatment with the sulphonyl chloride raise the m. p.

Morpholine derivative. Morpholine (4·4 g.) was added to a solution of *p*-cymenesulphonyl chloride (6 g.) in benzene (15c.c.). The morpholine hydrochloride which was immediately precipitated was filtered off, and the benzene removed in a vacuum at 30°. The resultant glass was triturated with light petroleum (b. p. 60—80°) and then recrystallised once from ethanol and twice from light petroleum. The *morpholide* formed white crystals, m. p. 62·5° (Found : N, 5·06. $C_{14}H_{21}O_3NS$ requires N, 4·95%).

Piperidine derivative. Piperidine (2 g.) was shaken with 10% sodium hydroxide (20 c.c.), and *p*-cymenesulphonyl chloride (9 g.) added in one-fifth portions. After being boiled for 30 minutes and kept overnight, the oily product was extracted with ether, and the extract washed and dried (Na_2SO_4). The ether was removed, and the oil distilled in a vacuum. The *piperidide*, b. p. 222—225°/15 mm., was colourless, but could not be induced to crystallise (Found : N, 5·00. $C_{15}H_{23}O_2NS$ requires N, 4·98%).

The authors thank the directors of Messrs. Muir and Pullar Ltd., Dunblane, Perthshire, for permission to publish this note, and Mr. A. L. Cochrane and Mr. T. J. M. Whitelaw, Analytical Dept., Distillers Co., Ltd., Glenochil, for the analyses.—THE DISTILLERS CO., LTD., GLENOCHIL, CLACKMANNANSHIRE. [*Received, December 20th*, 1949.]

Fluorescence and the Beer–Lambert Law. A Note on the Technique of Absorption Spectrophotometry.

By E. A. BRAUDE, J. S. FAWCETT, and C. J. TIMMONS.

ONE of the fundamental principles of quantitative absorption spectrophotometry is the assumption that the intensity of absorption is directly proportional to, and that the extinction coefficient is independent of, the concentration of absorbent (Beer's law) and the length of the absorption path (Lambert's law). As far as we are aware, the validity of Lambert's law has never been questioned. Deviations from Beer's law, on the other hand, are quite frequently encountered, but it appears generally accepted that this is always due to concentration-dependent chemical equilibria such as association or ionisation reactions. In general, however, simple organic compounds in neutral solution are assumed to obey the Beer–Lambert law, and in many cases the validity of the law has been tested and explicitly confirmed.

We have repeatedly observed (cf. Braude, Fawcett, and Newman, *J.*, 1950, 793) in the course of work with a wide variety of organic compounds, that the ultra-violet light absorption of substances which exhibit strong fluorescence in solution appears to vary markedly with both concentration and cell length. Moreover, smaller but nevertheless significant deviations from the Beer–Lambert law are found with many compounds which do not exhibit visible fluorescence, and the magnitude of the effects is closely dependent on the type of instrument and the experimental conditions employed. Although none of the compounds concerned would be expected to undergo any reversible reactions in dilute neutral solutions, such an explanation can never be rigidly ruled out for the deviations from Beer's law; the deviations from Lambert's law, on the other hand, which are equally or even more pronounced in these cases, can only be physical in origin. As will be shown in the sequel, it is very probable that the variations of extinction coefficient with concentration are due to the same cause as the variations with cell length, namely to the superposition of transmitted light and scattered fluorescence emission. This phenomenon appears to have escaped notice hitherto and the purpose of this note is to draw attention to the important bearing which it has on the widely employed techniques of absorption spectrophotometry.

Although relatively few quantitative measurements of the fluorescence spectra of organic compounds in solution have been recorded (cf. Hausser, Kuhn, and Kuhn, *Z. physikal. Chem.*, 1935, *B*, **29**, 417; Kortüm and Finckh, *ibid.*, 1942, *B*, **52**, 263; Ley and Specker, *Z. wiss. Photographie*, 1939, **38**, 13; Schoental and Scott, *J.*, 1949, 1683), it is known that unsaturated compounds which exhibit selective ultra-violet or visible-light absorption also give rise to fluorescence emission in the same region. Generally, the fluorescence spectrum is at longer wave-lengths than the absorption spectrum, but in polyatomic compounds some overlap often occurs owing to the close spacing of vibrational levels (cf. Bowen, *Quarterly Reviews*, 1947, **1**, 1). It is clear that if, in absorption measurements, any of the fluorescence emission reaches the recording device, the apparent intensity of transmitted light at that wave-length will be increased, *i.e.* the apparent intensity of absorption reduced, and that the magnitude of this effect will depend on the ratio of the intensities of the recorded fluorescence emission and of the transmitted light. It is necessary to distinguish between two types of instrument, (*a*) those in which the light is dispersed *after* passing through the absorbent (*e.g.* the Hilger Spekker spectrophotometer and most other photographic instruments) and (*b*) those in which the light is dispersed *before* passing through the absorbent (*e.g.* the Beckman and other photoelectric spectrophotometers). In type (*a*) a fraction of the fluorescence emission will be scattered into the slit of the spectrometer and will reach the recording device after dispersion, giving rise to an apparent decrease in absorption intensity at the wave-length of the *fluorescent* light. In this arrangement, the effect will be relatively small (*i.e.* only noticeable with strongly fluorescent substances or bands) and will be spread over the spectrum. It will be larger at high extinctions, when the intensity of real transmitted light is small, but the precise relationship between the extinction coefficient and the concentration and the cell-length may be influenced by at least the following additional factors : (i) decrease of fluorescence intensity at increasing concentrations owing to quenching effects, (ii) change in scattering properties with cell-length and cell shape, and (iii) increasing re-absorption of scattered fluorescence emissions with increasing cell-length. In instruments of type (*b*), the fluorescence emission will be scattered directly into the photoelectric cell, giving rise to an apparent decrease in absorption intensity at the wavelength of the *absorbed* light, and owing to the greater proximity of the cell to the recording device, the effect of the fluorescence emission will be much larger in this type of instrument than in type (*a*). As before, deviations from the Beer–Lambert law will be largest at high extinctions when the intensity of the transmitted light is small. The effect will therefore generally increase with increasing concentration at constant cell-length, and with increasing cell-length at constant concentration, subject to the additional factors mentioned above.

The fluorescence effect is illustrated below by measurements of the highest-intensity bands of naphthalene, anthracene, and styryldimethylcarbinol, using a Beckman photoelectric spectrophotometer (Model DU). Whereas potassium chromate gives concordant intensity values over the whole range of extinctions ($E = 0{\cdot}1$—$2{\cdot}5$) and cell lengths (0·1—1·0 cm.) employed, the apparent extinction coefficients for the organic compounds show startling variations, ε decreasing strongly at high extinctions The deviations from the Beer–Lambert law generally become appreciable for extinctions above 1·0, and for extinctions higher than 2·0, ε actually decreases with increasing concentration in the case of naphthalene and anthracene. Under these conditions, the intensity of the fluorescent light is evidently greater than that of the transmitted light and therefore the fluorescent intensities in these examples are of the order of one hundredth of the intensity of the incident light. As would be expected, extinction readings in the region where the fluorescence effect is appreciable vary somewhat with the slit width employed. Deviations of a smaller order are also exhibited by the longer-wave-length, lower-intensity bands of napthalene and anthracene. Using a Hilger Spekker photographic spectrophotometer, on the other hand, the Beer–Lambert law is obeyed almost within experimental error (±2%) in agreement with the findings of Mayneord and Roe (*Proc. Roy. Soc.*, 1935, *A*, **152**, 299) and the extinction coefficients correspond fairly closely to the highest values of ε obtained with the photoelectric instrument.

The results obtained with styryldimethylcarbinol show that the fluorescence effect is by no means limited to polycyclic aromatic derivatives (cf. Braude, Fawcett, and Newman, *J.*, 1950, 793). Since all compounds exhibiting selective absorption in the ultra-violet may theoretically also exhibit fluorescence, deviations from the Beer–Lambert law would indeed be expected to be quite general, but the magnitude of the effect will obviously depend on the wave-lengths and the intensities of the fluorescence bands and little is known at present concerning the dependence of fluorescence on structure in simple unsaturated systems. Using a Beckman instrument, we have observed appreciable deviations from the Beer–Lambert law with other styryl derivatives, but not with benzoic acid or conjugated acyclic dienes.

These findings are of obvious significance in relation to the use of light-absorption data for the characterisation and analysis of organic compounds and in relation to the choice and design of instruments. It is evidently desirable that the Beer–Lambert law should be tested wherever possible and that the conditions of measurement should be more closely defined than has been the practice hitherto. The extinction range $E = 0{\cdot}3$—$0{\cdot}7$ is usually regarded as instrumentally the most accurate in photoelectric photometry, and the possibility of fluorescence emission provides additional reason for avoiding higher extinctions.

Beckman Photoelectric Spectrophotometer.

c = Concentration in g.-mols./l. l = Cell length in cm. E = Extinction (optical density) reading. ε = Apparent molecular extinction coefficient = E/cl

(i) Potassium chromate in 0·05M-aqueous potassium hydroxide. Maximum at 2725 A.

10^4c	0·285	0·700	2·08	4·87	5·58	3·48				
l	1·0					0·1	0·2	0·33	0·5	1·0
E	0·104	0·251	0·748	1·75	2·38	0·123	0·248	0·423	0·625	1·23
ε	3,660	3,580	3,580	3,540	3,620	3,540	3,560	3,640	3,580	3,620

(ii) Naphthalene in ethanol. Maximum at 2200 A.

10^4c	0·012	0·065	0·15	0·25	0·35	1·55	0·47			
l	1·0						0·1	0·2	0·33	0·5
E	0·119	0·618	1·39	2·05	2·35	2·32	0·518	1·16	1·69	2·28
ε	99,000	95,000	93,000	82,000	67,000	15,000	110,000	108,000	108,000	97,000

(iii) Anthracene in ethanol. Maximum at 2510 A.

10^4c	0·011	0·033	0·055	0·099	0·132	0·154	0·275	0·860	1·38	4·50
l	1·0									
E	0·188	0·565	0·930	1·537	1·805	1·965	2·15	2·22	2·23	2·21
ε	170,000	171,000	170,000	156,000	142,000	128,000	78,500	27,000	16,000	4,900

10^4c	2·75				
l	0·1	0·2	0·33	0·5	1·0
E	0·473	0·933	1·558	1·860	2·05
ε	172,000	170,000	170,000	136,000	74,500

(iv) Styryldimethylcarbinol in 60% aqueous dioxan. Maximum at 2510 A.

10^4c	0·11	0·29	0·55	1·10	4·27	2·14				
l	1·0					0·1	0·2	0·33	0·5	1·0
E	0·212	0·535	0·946	1·53	1·75	0·394	0·738	1·20	1·685	1·74
ε	19,300	18,500	17,200	13,900	4,100	18,400	17,200	16,800	14,800	8,100

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The Dinitrophenylhydrazones of the Halogenobenzaldehydes. By O. L. BRADY and S. G. JARRETT.

WHILE the various halogenobenzaldehydes were available in connection with other work their 2 : 4-dinitrophenylhydrazones have been prepared by addition of the aldehyde (2 g.), dissolved in a small quantity of alcohol, to a hot solution of 2 : 4-dinitrophenylhydrazine sulphate [prepared by the addition of concentrated sulphuric acid (4 c.c.) to a suspension of 2 : 4-dinitrophenylhydrazine (2 g.) in alcohol (50 c.c.)] whereupon the dinitrophenylhydrazones separated. They crystallised from xylene in orange crystals except where otherwise stated. In place of the aldehydes the oximes can be used; as these can be purified by crystallisation, purer products can be obtained from them than from the liquid aldehydes.

$XC_6H_4{\cdot}CH{:}N{\cdot}NH{\cdot}C_6H_3(NO_2)_2$.

		Found, %,				Found, %,				Found, %,	
X.	M. p.	C.	H.	X.	M. p.	C.	H.	X.	M. p.	C.	H.
o-F	200°	51·8	3·0	*o*-Br	203°	43·2	2·6	*o*-I	215°	38·5	2·2
m-F	266	51·5	2·8	*m*-Br	257	43·1	2·5	*m*-I	258	38·2	2·3
p-F	278	51·2	3·0	*p*-Br	257	42·9	2·8	*p*-I *	258	38·3	2·2

($C_{13}H_9O_4N_4F$ requires C, 51·3; H, 3·0%.) ($C_{13}H_9O_4N_4Br$ requires C, 42·7; H, 2·5%.) ($C_{13}H_9O_4N_4I$ requires C, 37·9; H, 2·2%.)

* Scarlet crystals.

The dinitrophenylhydrazones of the chlorobenzaldehydes have been described by Blanksma and Wacker (*Rec. Trav. chim.*, 1936, **55**, 658), Ferranti and Bloom (*Amer. J. Pharm.*, 1933, **105**, 381), Eitel and Lock (*Monatsh.*, 1939, **72**, 289), and Graymore and Davies (*J.*, 1945, 293). The melting points of our specimens were: *o*-compound 210° and *m*-compound 255°, which are within 1° of the values given by Blanksma and Wacker but considerably different from those of some other workers. For the *p*-chloro-compound (Found: C, 49·1; H, 2·8. Calc. for $C_{13}H_9O_4N_4Cl$: C, 48·7; H, 2·8%) we find m. p. 266° as compared with 216°, 224°, and 218—220° given by other workers. It seems probable that our compound was an isomeric form like others previously noticed among dinitrophenylhydrazones. It may be noted that the melting points given by other workers for the *p*-compound are between those for the *o*- and *m*-derivatives, which is contrary to general experience with compounds of this type.—THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES, UNIVERSITY COLLEGE, LONDON. [*Received, January* 17*th*, 1950.]

OBITUARY NOTICE.

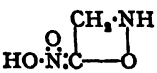
SIR WYNDHAM ROWLAND DUNSTAN.

1861—1949.

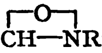
Sir Wyndham Rowland Dunstan, K.C.M.G., LL.D., F.R.S., died on April 20th, 1949, at the age of 87. He was the son of John Dunstan, Constable and Governor of Chester Castle, and was born at Chester on the 24th May, 1861. He was educated at Bedford School and abroad and began his chemical career at the early age of 18 by becoming assistant to Theophilus Redwood, then Professor of Chemistry at the School of Pharmacy of the Pharmaceutical Society. When this post was divided by the allocation of laboratory work to Professor John Attfield, Dunstan became a demonstrator under Attfield. In 1884 he moved to Oxford having been appointed a demonstrator in the University Chemical Laboratories, and in the following year he was made University Lecturer in Chemistry in Relation to Medicine, a post he retained for some years after succeeding Redwood as Professor of Chemistry in the Pharmaceutical Society's School in 1886. From 1892 to 1900 he was also lecturer in chemistry at St. Thomas's Hospital Medical School, a post he kept for four years after his appointment as Director of the Scientific and Technical Department of the Imperial Institute in 1896. Seven years later he succeeded Sir Frederick Abel in the full Directorship of the Institute, where he remained until his retirement from active work in 1924.

Dunstan's early work was concerned almost wholly with the development of processes for the assay of active components in the natural drugs of the British Pharmacopoeia, and with the application of the results to the production of galenical preparations of these drugs, such as tinctures and extracts, in a standardised form, *i.e.*, containing a specified percentage of the active substance. This was due to the fact that the 1874 Pharmacopoeia was then under revision, Redwood being one of the responsible editors, and the necessary experimental work had to be done in his laboratory. Dunstan had a practical bent of mind well suited to such investigations, as is shown by his work on nux vomica with F. W. Short and on solanaceous drugs with F. Ransom and A. E. Chaston. Nine papers were published on nux vomica of which the most interesting are probably that on the isolation of the crystalline glucoside, loganin, from the pulp of nux vomica fruit (*Pharm. J.*, 1884, [iii], **14**, 1025) and that dealing with the quantitative separation of strychnine and brucine, based on the precipitation of the former as ferrocyanide and recovery of the alkaloid, as adopted in the Pharmacopoeia of 1898. Four papers on the assay of alkaloids in belladonna leaves and root and on the standardisation of their preparations were published by Dunstan and Ransom (*ibid.*, 1884, [iii], **14**, 623; 1884, [iii], **15**, 154; 1885—6, [iii], **16**, 237, 777; 1887, [iii], **17**, 843), and special attention was given to the rhizome of *Scopola carniolica* from which Dunstan and Chaston isolated hyoscyamine, possibly a minute amount of hyoscine, a phytosterol, arachidic acid from the fat, dextrose, and scopoletin (*ibid.*, 1889, [iii], **20**, 461). This drug was at that time regarded as a possible substitute for belladonna, and a group of workers published papers on it: E. M. Holmes on its natural history; T. Greenish on the histology; F. Ransom on its pharmacy; and Sir Dyce Duckworth on the therapeutic action (*ibid.*, pp. 468, 471, 464, 466).

Dunstan also set out to improve the two alkyl nitrite preparations of the Pharmacopoeia and to that end prepared in collaboration with T. S. Dymond, E. J. Woolley, and W. Lloyd Williams (*ibid.*, 1888, [iii], **18**, 861; **19**, 485, 487, 489, 741) the homologous series from methyl to *n*-, *sec.*-, and *tert.*-amyl nitrites, which were examined pharmacologically by Professor J. T. Cash, who, in addition to a number of conclusions which have since become familiar features of pharmacological action in homologous series, showed that the action of the nitrites is not solely, or even mainly in some cases, caused by the amount of nitroxyl (NO_2) they contain, and suggested that the simple nitrites attached themselves more readily to certain constituents of blood and muscle and so acted more quickly, whilst their greater stability ensured longer duration of action (Cash and Dunstan, *Phil. Trans.*, 1893, *B*, **184**, 505). A side issue of this work was the observation by Dunstan and Dymond (*Proc. Chem. Soc.*, 1888, 117; *J.*, 1891, **59**, 410) that the action of alkali on nitroethane produces acetonitrile, nitrous acid, and 3 : 4 : 5-trimethyl*iso*oxazole, the last a type of compound first prepared by Claisen and Lowman (*Ber.*, 1888, **21**, 18, 1149). With nitromethane, alkalis produce, not an *iso*oxazole, but methazonic acid, $C_2H_4O_3N_2$, a substance first obtained by Lecco (*Ber.*, 1876, **9**, 705). It was prepared and examined by Dunstan and



Goulding (*J.*, 1900, **77**, 1262) who, mainly on the ground that on hydrolysis by alkali or acid it produced carbon dioxide, hydroxylamine, and hydrocyanic acid, proposed for it the annexed formula, but shortly afterwards Scholl (*Ber.*, 1901, **34**, 862) suggested that it might be regarded as a nitrogen analogue of acetoacetic acid and formulated as $CH_2\text{:}NO\cdot CH\text{:}NO\cdot OH$, and later Meister (*Ber.*, 1907, **40**, 3435) recorded a number of new reactions for the acid and claimed that it could be represented as $HON\text{:}CH\cdot CH_2\cdot NO_2$, or as its conjugated tautomeride $HO\cdot N\text{:}CH\cdot CH\text{:}NO\cdot OH$.

About this time the long-continued discussion on the isomerism of aldoximes was beginning and Dunstan and Dymond showed that acetaldoxime, b. p. 114·5°, was a mixture of two forms, one crystalline, m. p. 46·5°, and the other liquid, of which the latter was not obtained quite free from its isomeride. Both were interconvertible and much less stable than the two benzaldoximes but such experimental evidence as could be obtained indicated that they corresponded to the *anti-* and *syn*-aldoximes respectively. Propaldoxime and *iso*butaldoxime were also each separated into *anti-* and *syn*-forms (*J.*, 1892, **61**, 470; *Proc. Chem. Soc.*, 1892, 135; *J.*, 1894, **65**, 206; cf. Carveth, *J. Physical Chem.*, 1898, **2**, 159). In the period 1896—1901, in collaboration with E. Goulding, Dunstan published six papers dealing with the action of alkyl halides on hydroxylamine and on oximes. With the former, action is most complete with methyl iodide, which produces di- and tri-hydroxylamine hydriodides, and trimethylhydroxylamine hydriodide, $(CH_3)_3NO,HI$, later called trimethyloxamine or trimethylamine oxide hydriodide. With ethyl, *n*-propyl, or *iso*propyl iodide only the dialkylhydroxylamine is formed at the first stage but the triethyl compound can be got by further action of the alkyl iodide, though this does not happen with the di-*n*-propyl and di*iso*propyl compounds. These trialkylated substances were the first examples of aliphatic amine oxides, and it was later found that they could be produced by the action of hydrogen peroxide on trialkylamines and that by like means dialkylamines could be converted into the dialkylhydroxylamines $(Alk)_2N\cdot OH$, except in the case of dimethylamine, which instead was oxidised to formaldehyde and formic and nitrous acids (*J.*, 1896, **69**, 839; 1899, **75**, 792, 1004; 1901, **79**, 641). Also, with E. Goulding as collaborator, Dunstan investigated the action of alkyl iodides on a series of aldoximes and ketoximes alone and in presence of sodium methoxide in methyl alcohol. In the former case *N*-alkyl derivatives, then represented as alkyl*iso*oximes, *e.g.*, the alkyl*iso*aldoximes  $R\cdot CH\text{—}NR'$, were alone formed, whereas in presence of alkali the isomeric ethers, *e.g.*, the alkylaldoximes, $R\cdot CH\text{:}N\cdot OR'$, were also produced, the relative proportions of the two isomerides varying with the nature of the oxime and the alkyl iodide used (*J.*, 1897, **71**, 573; 1901, **79**, 628).

Of the remaining investigations probably the most important is that of the aconite alkaloids, on which eighteen papers were published during 1891—1905, with several collaborators, notably W. H. Ince, J. C. Umney, F. W. Passmore, F. H. Carr, H. A. D. Jowett, E. F. Harrison, T. Tickle, H. M. Read, and A. E. Andrews. The early workers on aconitine, Alder Wright in this country and Jurgens in Germany, adopted for the alkaloid the formula $C_{33}H_{43}O_{12}N$ or $C_{33}H_{47}O_{12}N$, and $C_{33}H_{45}O_{12}N$ was found by Dunstan and Ince. Up to that time aconitine had been regarded as benzoylaconine, isomeric with the substance variously named picraconitine, isaconitine, or benzaconine. In 1892 Ehrenburg and Purfurst (*J. pr. Chem.*, 1892, **45**, 604) showed that, when heated dry, aconitine loses acetic acid, and this was later confirmed by Dunstan and Carr (*J.*, 1894, **65**, 176) who isolated and characterised the resulting pyraconitine, $C_{31}H_{41}O_{10}N$. Meanwhile Freund and Beck (*Ber.*, 1894, **27**, 433, 720) had found that the empirical formula of aconitine should be $C_{34}H_{47}O_{11}N$, which after some discussion was accepted by the English workers, and both protagonists agreed that aconitine was acetylbenzoylaconine. It thus became the prototype of the highly toxic diacylaconines characteristic of many aconites of which pseudaconitine from Nepaul aconite was shown to be acetylveratroylpseudaconine (Dunstan and Carr, *J.*, 1897, **71**, 350), indaconitine from *A. chasmanthum* to be acetylbenzoylpseudaconine (Dunstan and Andrews, *J.*, 1905, **87**, 1620), bikhaconitine from *A. spicatum* to be acetylveratroylbikhaconine (Dunstan and Andrews, *ibid.*, p. 1636), and japaconitine from Japanese aconite to be acetylbenzoyljapaconine (Dunstan and Read, *J.*, 1900, **77**, 49). All these alkaloids and certain of their derivatives were examined pharmacologically by Professor Cash, and the detailed results communicated to the Royal Society (Cash and Dunstan, *Phil. Trans.*, 1898, *B*, **190**, 239; 1902, B, **195**, 39, 97; *Proc. Roy. Soc.*, 1905, *B*, **76**, 468; see also Cash, *Brit. Med. J.*, 1908, I, 1213).

The series of papers on " Cyanogenesis in Plants " arose out of the poisoning of domestic animals in Egypt by *Lotus arabicus*, a plant which when fully ripe is collected by the Arabs as fodder for cattle but which had long been known to be poisonous in the early stages of growth.

It was found that dried immature plants when ground and moistened with water produced a strong odour of prussic acid. This cyanogenetic action was traced to the action of an enzyme, lotase, on a glucoside, lotusin, which produced prussic acid, dextrose, and a yellow pigment, lotoflavin (Dunstan and Henry, *Phil. Trans.*, 1901, *B*, **194**, 515). It was not easy in those days to get collected in good condition the considerable supply of material required for chemical examination and though a fair quantity of this plant became available it arrived in small quantities, in which the yield of prussic acid varied, and the plant was sometimes mature enough to yield only traces. The total amount of lotusin obtained was small in comparison with the yield of prussic acid from dried young plants in good condition, and this deficiency is still not accounted for in the preliminary account of a re-examination of the plant started just before the outbreak of war (Henry, *J. Soc. Chem. Ind.*, 1938, **57**, 248), in which a well-defined pigment glucoside, $C_{22}H_{24}O_{11}$, was isolated along with the cyanogenetic glucoside, lotaustralin, which Finnemore, Cooper, and Stanley (*ibid.*, p. 162) first obtained about the same time from the related plant *Lotus australis* var. *pubescens*. In this second investigation in which acetone was used as the extracting medium in place of alcohol, no lotusin was isolated but the residual extracts still contained much cyanogenetic material. The second plant examined was " dhurra " (*Sorghum vulgare*) from Egypt. In this case also the toxic substance disappears as the plant matures and there is none in the seed, which is a common tropical food-grain. The cyanogenetic glucoside in this case was named " dhurrin " and proved to be a glucoside of *p*-hydroxybenzaldehyde cyanohydrin. An easier material to deal with was the seeds of *Phaseolus lunatus*, which as collected from the semi-cultivated plant, grown as a green manure in Mauritius, are brown with violet patches and poisonous, as distinct from the white and harmless " Lima beans," yielded by the carefully cultivated plant. Previous observations by Bonamé in Mauritius and by van Romburgh in Java had shown that this plant when crushed, moistened with water, and distilled yielded acetone and prussic acid. The formation of these products was traced to the action of an enzyme on phaseolunatin, which proved to be a glucoside of acetone cyanohydrin (Dunstan and Henry, *Proc. Roy. Soc.*, 1903, *B*, **72**, 285) which was later also isolated from cassava root and from young flax plants (Dunstan, Henry, and Auld, *Proc. Roy. Soc.*, 1906, *B*, **78**, 145, 152; 1907, **79**, 315), and the linamarin obtained from flax by Jorissen and Hairs (*Bull. Acad. Roy. Belg.*, 1891, [iii], **21**, 529) was shown to be identical with phaseolunatin.

Among other natural products examined mention may be made of the Egyptian plant *Hyoscyamus muticus*, which was shown to contain hyoscyamine without hyoscine (Dunstan and Brown, *J.*, 1899, **75**, 72) and has now for many years been a commercial source of atropine.

Dunstan also made an excursion into inorganic chemistry in a group of papers on the rusting of iron, in which he maintained that the essential condition for the aerial oxidation or rusting of iron and other metals is the simultaneous presence of oxygen and liquid water, that carbon dioxide facilitates but does not initiate the process, and that agents such as alkalis, potassium dichromate, sodium nitrite, and potassium ferrocyanide, which prevented, to a greater or less extent, the formation of rust were also agents in whose presence the decomposition of hydrogen peroxide occurs, from which he deduced that hydrogen peroxide is an essential intermediary in the formation of rust and that in the case of iron the process may be represented :

$$Fe + O_2 + H_2O = FeO + H_2O_2; \quad 2FeO + H_2O_2 = Fe_2O_2(OH)_2.$$

Though this view (*Proc. Chem. Soc.*, 1903, **19**, 150) was supported by much experimental evidence (Dunstan, Jowett, and Goulding, *J.*, 1905, **93**, 1548) it led to considerable discussion. Up to that time the findings of Grace Calvert (*Manchester Lit. Phil. Mem.*, 1871, **5**, 104) as interpreted by Crum Brown (*J. Iron Steel Inst.*, 1888, 129), that rusting was due to the combined action of the carbon dioxide and oxygen of the air, had not been questioned and it was assumed that the iron carbonate first formed was gradually converted into a ferric hydroxide or rust by the further action of atmospheric oxygen. That theory was now supported by G. T. Moody and his notes led to interesting discussions at meetings of the Society (*Proc. Chem. Soc.*, 1903, **19**, 157, 239, 273; 1906, **22**, 101; 1907, **23**, 84; 1909, **25**, 34; *J.*, 1906, **89**, 720; cf. Dunstan, *Proc. Chem. Soc.*, 1907, **23**, 63). An electrolytic explanation of the corrosion of iron was advanced by Whitney (*J. Amer. Chem. Soc.*, 1903, **25**, 394) and received some support from Walker, Cederholm, and Bent in the United States (*ibid.*, 1907, **29**, 1251) and from Tilden in this country (*J.*, 1908, **93**, 1356). Experimental evidence against both these theories was provided by Dunstan *et al.* (*loc. cit.*) and, in returning to the subject, Dunstan and J. R. Hill (*J.*, 1911, **99**, 1835, 1853) emphasised that " none of the existing theories adequately explains how the various inhibiting agents prevent rusting " and in the first of the two papers quoted they record the results of a number of new experiments showing that all these inhibitors act by rendering iron

" passive " and that this passivity persists after removal of the iron from the solution causing it. It was also suggested that, as potassium iodide and certain other reducing agents destroy hydrogen peroxide and yet do not inhibit rusting, the peroxide is probably not an intermediate product of the main reaction as originally postulated but may be the result of a secondary reaction, since oxidation can apparently proceed without its formation, and they conclude that " metals undergo aerial oxidation by direct action of oxygen dissolved in water."

In 1899, largely under Dunstan's influence, a Research Laboratory was inaugurated by the Pharmaceutical Society, by addition to their premises in Bloomsbury Square, and most of the work referred to above was started in that institution and was transferred to, and continued in, the Scientific and Technical Department of the Imperial Institute when Dunstan moved there in 1896. The Institute was founded to commemorate the fiftieth year (1887) of Queen Victoria's reign and was opened by Her Majesty in 1893, by which time some progress had been made in installing in the Public Exhibition Galleries representative collections of the natural products of the Colonies and India, and it was possible to begin giving attention to the second objective of the Institute, the scientific examination of new or little known products from the Overseas Empire. The Institute was severely handicapped by lack of funds but the first Director, Sir Frederick Abel, found it possible to secure the co-operation of a number of eminent men of science, who undertook to examine in their own laboratories materials provided by the Institute. Much useful work was done under this arrangement, *e.g.*, by Dr. A. W. Crossley and Mr. Le Sueur on Indian vegetable oils, by Professor W. C. Unwin on mechanical tests of new timbers, by Professor A. H. Church on the composition of Indian food-grains, by Messrs. Cross and Bevan on new fibres, and by Professors A. G. Perkin and J. J. Hummel respectively on the components and the tinctorial properties of Indian dye-stuffs. This arrangement was continued when, thanks to the generous financial help provided by the Commissioners of the 1851 Exhibition, the Goldsmiths' and Salters' Companies and other donors, it was possible to equip and operate the laboratories of the Scientific and Technical Department on Dunstan's assumption of the Directorship in 1896. During the first few years it was still possible to carry on mainly detailed investigations such as those already referred to, but as the facilities offered by the Institute for the examination of natural products became better known in the Colonies and India, thanks to Dunstan's organizing ability and driving power, the character of the work done had perforce to change, as will be seen in the volume of " Technical Reports and Scientific Papers " published by the Imperial Institute in 1903, which opens with an interesting preface by Sir Frederick Abel describing the inception of the Institute and the objectives which its founders had in view. Part I of the volume is a series of reports on coals, iron ores, mica, and other minerals, followed by collected reports on fibres, edible and essential oils and oil-seeds, rubber and gutta percha, gums and resins, medicinal plants and tobacco, tanning and dyeing materials, fodder plants and food-grains, and timbers, many of the items being provided by the scheme of co-operation with the external expert referees referred to above. From 1903 the more important technical reports of the Department were published in the quarterly *Bulletin of the Imperial Institute* but in the period 1909—1914 a further group of five collected reports, with Dunstan as responsible editor and dealing with Fibres, Gums and Resins, Foodstuffs, Rubber and Gutta Percha, and Oil-seeds, Oils, Fats, and Waxes, was issued in the Miscellaneous Series of Colonial Reports. Also printed in this series was the " Report on British Cotton Cultivation," which with Dunstan's prior " Report to the Board Trade on Cotton Cultivation in the British Empire and Egypt " (1904) indicates the part played by the Imperial Institute, when, in the early years of this century, there was a prospective shortage of raw cotton and strenuous efforts were made to increase cultivation of this commodity within the Empire. In the same connection Dunstan also paid official visits to Cyprus and Asia Minor and prepared reports, published in the same series, on the agricultural resources of those areas with special reference to cotton cultivation. He was also responsible for another important development in the exploration and utilisation of Colonial natural resources, *viz.*, the institution of Mineral Surveys in Ceylon, Southern Nigeria, Northern Nigeria, and Nyasaland. These were conducted by geological surveyors operating in the territories named, and the mineral samples collected by them were sent to the Imperial Institute for mineralogical and chemical examination. Reports on this work were also published in the Miscellaneous Series of Colonial Reports. Among the more interesting results were the discovery of thorium minerals, especially the new mineral thorianite (Dunstan, *Nature*, 1904, **69** 510; with G. S. Blake, *Proc. Roy. Soc.*, 1905, *A*, **76**, 253; with B. M. Jones, *ibid.*, 1906, *A*, **77**, 346) in Ceylon by Dr. Coomaraswamy, the location of beds of lignite and of the now important Udi coalfield in Southern Nigeria by Mr. A. E. (later Sir Albert) Kitson, and of deposits of iron ore in Northern Nigeria by Dr. J. D. Falconer who subsequently became Director of the Geological

Survey of Nigeria and is the author of a monograph on "The Geology and Geography of Northern Nigeria."

Dunstan also considered the publication of information regarding the natural resources of the Overseas Empire as an important function of the Imperial Institute, and a section of the quarterly *Bulletin* was always allocated for this purpose. This also was the idea behind three series of publications issued by Mr. John Murray, namely:

" The Imperial Institute Handbooks to the Commercial Resources of the Tropics," of which four volumes were issued with Dunstan as Editor.

" The Imperial Institute Monographs on Mineral Resources with special reference to the British Empire." Fifteen of these, each dealing with one set of minerals, were prepared under the direction of the Mineral Resources Committee of the Imperial Institute.

A series of reports on rice, lac, turpentine, oil-seeds, etc., resulting from the Indian Trade Enquiry authorised by the Secretary of State for India in 1916.

The *Bulletin of the Imperial Institute* for 1923 contains a long and detailed " Report on the Operation of the Imperial Institute," which deals with the organization and work of the Institute up to a date shortly before Dunstan's retirement. It is an interesting account of the foundation and progress of an organisation concerned with this important phase of colonial economic development, to which he devoted nearly two-thirds of his working life.

Dunstan was a Fellow of the Chemical Society for 70 years, having joined in 1879; he served on the Council in 1889 to 1891 and was Secretary from 1893 to 1903 and a Vice-President from 1904 to 1906. He became a Fellow of the Royal Society in 1893 and was a member of the Council from 1905 to 1907. He presided over the Chemical Section of the British Association at the meeting held in York in 1906. In 1910 he became President of the International Association of Tropical Agriculture, which had its headquarters in Paris, and in that capacity was President of the Third International Congress of Tropical Agriculture, held at the Imperial Institute in 1914, just before the outbreak of the First World War. He also served on the Council of the Royal Geographical Society in 1916. Dunstan was fond of travel. As already mentioned he visited Cyprus in 1904 and Asia Minor in 1907 at the request of the Colonial Office and, at the invitation of the respective governments, he undertook similar missions to Ceylon in 1910 and 1914, India in 1914, and Newfoundland in the same year.

Dunstan was an excellent lecturer and in his teaching days was always popular with his students. He was interested in education, especially in science teaching, and this led to his service as Secretary of the British Association Committee dealing with that subject from 1887 to 1891. It was also no doubt this interest which led to his serving at various times on the governing bodies of constituent colleges of London University and to his becoming a Vice-President of the Girls' Public Day School Trust.

Dunstan was also concerned with philosophy and in an article on " Our Quest for Philosophy and what came of it," contributed to the *Hibbert Journal* for July 1942, he describes his association with Dr. Alfred Senier in the foundation of the Aristotelian Society of which he was one of the first three Vice-Presidents, and for a time he edited the Society's *Proceedings.*

He was also an honorary member of the Institut Egyptien, and a Commander of the Order of Leopold of Belgium.

He was made C.M.G. in 1913 and K.C.M.G. on his retirement in 1924.

Dunstan was married twice, in 1886 to Emilie Fordyce Maclean, who died in 1893 leaving a son and a daughter, and in 1900 to Violet Hanbury-Tracy, who survives him with a second daughter.

T. A. HENRY.

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